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Abstract

This IDEA grant proposal tested the feasibility of a regimen of conformal hypo-fractionated radiotherapy (5 fractions in 2 weeks) directed to the original tumor bed with margins in a selected subset of post-menopausal women with breast cancer with a very low risk for local recurrence elsewhere in the breast. The relevance of this approach consists of the fact that if proven equivalent in efficacy it would be more patient-friendly (30 fractions over 6 weeks) convenient and economical.

This final report demonstrated feasibility in all 63 patients accrued to the trial, with minimal acute side effects. Among the 53 patients with at least 6 months follow-up late effects were limited to the rare occurrence of modest fibrosis and teleangectasia. With a median follow up of 24 months, in none of the patients breast cancer has recurred.

Prone partial breast radiotherapy, delivered by an external beam simple technique over 5 fractions was feasible and very well tolerated. These results need to be confirmed in a larger cohort of patients, ideally in a multi-institutional setting.

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INTRODUCTION:

Since in a selected subset of post-menopausal women with breast cancer there is a very low risk for local recurrence elsewhere in the breast, a regimen of conformal hypo-fractionated radiotherapy (5 fractions in 2 weeks) directed to the original tumor bed with margins, could generates local control rates and cosmetic results equivalent to those achieved by conventional post-operative radiotherapy (30 fractions over 6 weeks) while being much more convenient and economical.

The specific aims of this IDEA grant are:

1. To determine the feasibility of a regimen of hypo-fractionated conformal radiotherapy to the tumor bed as part of breast preservation in selected post-menopausal women with T1 breast cancers.
2. To explore the efficacy of this approach when compared to historical local control rates achieved by standard post-operative radiation.
3. To prospectively assess the role of circulating TGF-β pre-treatment as a marker for post-treatment fibrosis.
4. To pilot-test the use of ultrasound for localizing the radiation therapy target (tumor bed) and for daily positioning of the target with respect to the linear accelerator's radiation beams

BODY:

The study expected to accrue a total of 99 patients in 4 years.

Because of the study design, that requires for patient to first refuse to undergo standard radiotherapy to be offered the protocol, only 63 patients were accrued over 4 years.

An NYU–IRB approved protocol testing the research hypothesis of this study has been actively recruiting patients since October 2000, with independent funding from those allocated by the current award. The first 29 patients have been accrued according to the protocol and consent IRB-approved at NYU and originally submitted to the DOD, since the modifications to the protocol and the consent required by the DOD were minor and have not modified the research component of the trial. The remaining patients have been accrued according to the amended protocol and consent that reflects the minor changes required by the DOD-IRB.

We are hereby reporting the results obtained in 63 patients accrued. The study continues accrual to a total of 99 patients, as planned. Support for data managing and nursing is provided by the Research Fund of the NYU Faculty Group Practice.

With regard to Task 1 and 2 of the approved statement of work: (year 1-4)

"To determine the feasibility of a regimen of hypo-fractionated conformal radiotherapy to the tumor bed as part of breast preservation in selected post-menopausal women with T1 breast cancers, and to explore the efficacy of this approach when compared to historical local control rates achieved by standard post-operative radiation."

At the time of the current report 63 patients have accrued (median age 67.5 years, range: 51 to 88). The median tumor diameter is 1 cm (range 0.2-1.9). Sixty-two/63 patients completed treatment and are available for follow-up. One patient refused further treatment after 2 fractions for personal reasons, as previously reported. This patient

remains in communication with her primary doctor and she is reported to be NED three years later.
All 63 appear to tolerate treatment very well with only mild discomfort reported when lying prone for planning and treatment.
The most common acute toxicity was grade 1-2 erythema (46%) occurring in the treatment portal and fatigue (15 patients), usually manifesting in the second week of treatment. Two patients reported Grade 1-2 nausea. Two patients developed Grade 1 dry desquamation and one patient grade 1 breast edema. Six patients had induration at the surgical scar, pre-dating radiation therapy.
There are 53 patients who have $\geq$ 6 months follow-up. Preliminary assessment of late toxicity, included 14 patients who developed 17 events, including grade 1-2 induration (5 patients), fibrosis (1 patient), breast edema (2 patients), teleangectasia (5 patients), hyperpigmentation (4 patients).
Among the 63 patients who have completed treatment no recurrence have occurred: median follow up is 24 months.

During this first phase of the trial we have focused on two tasks:

1) designing a more comfortable and reliable treatment table that can enable geriatric breast cancer patients to comfortably withstand the treatment in prone position.

As a result of a partnership with one of our breast cancer survivor/advocate who is an architect, a new, much more comfortable table for prone imaging and treating was designed (designing and engineering was generously donated by our partner-advocate) and built, as per the attached digital photo (see appendix). The table underwent testing (2).

2) developing preliminary **physics data about dose volume histogram (DVH) analysis** in the studied population.

Much of our initial research effort has been spent in studying geometric and anatomic issues of the tested technique and their dosimetric implications.
As described in the original proposal the breast tissue and tumor bed, identified at CT as the post-surgical cavity, are contoured on a 3D planning system (Varian Somavision/CadPlan) and a 2 cm margin added to determine the PTV. A plan was generated in the attempt to treat the entire PTV to 90% of the prescription dose. Six Gy per fraction are delivered to the 95 % isodose surface in 5 fractions over ten days weeks. to a total dose of 30 Gy.
Planning in the prone position was feasible in 59 patients. Four patients were treated in the supine position (as accepted protocol deviations), 2 patients were unable to tolerate lying in the prone position secondary to paraplegia and 2 patients, the position of the tumor bed was located very lateral and better treated supine. The predominant technique for treatment was a pair of parallel-opposed mini-tangents. This arrangement assured good coverage given the constraints imposed by the PTV and its relationship to the table. For the entire group the volume of breast receiving 30 Gy ranged from 10% to 45%. We found heterogeneity of DVH based on the position of the original tumor bed and the size

of the breast. In 16 of the 63 patients, in order to successfully treat the PTV, greater than 50% of the ipsilateral breast volume received >50% of the prescription dose. This was largely dependent on the size of the tumor bed and its location in comparison to the index breast. Doses to the heart and lungs were clinically insignificant.
In conclusion, these preliminary data confirm in that in most cases (47/63) it is possible to successfully plan and treat the PTV with parallel opposed tangent fields without exceeding 50% of the dose to 50% of the breast volume.

Task 3: (year 1-4)
To prospectively assess the role of circulating TGF-β pre-treatment as a marker for post-treatment fibrosis.

As planned, patients were seen once/week during treatment and once two weeks after. Thereafter they will be seen in follow up every 3 months for the first year and every six months for the following five years. At each visit, physical exam to detect clinical recurrence was performed and mammography films (once/year) were reviewed. The data has been regularly collected in the Oracle forms specifically developed for data collection and submitted with the previous annual report. Since post-radiotherapy breast fibrosis evolves over time and generally achieves a "plateau" at 24 to 30 months, we are planning to assess the incidence of fibrosis when 50% of the patients have reached the 24 months minimum follow up, i.e. when at least 50 patients are available for evaluation after 24 months from treatment (based on our original design, with a planned accrual of 99 patients). We expect to reach this point in the next 6 months.

Task 4: (year 1-2)
To pilot-test the use of ultrasound for localizing the radiation therapy target (tumor bed) and for daily positioning of the target with respect to the linear accelerator's radiation beams.

We had planned to establish the accuracy in target definition by ultrasound imaging and to compare it to CT imaging. Since the necessary funding for the acquisition of the US device was obtained only one year ago, only CT imaging was used for the first 47 patients accrued to the trial. Comparison of US and CT for determination of the cavity was conducted in 5 patients and demonstrated superiority of CT.

KEY RESEARCH ACCOMPLISHMENTS:

1. feasibility is demonstrated in the first 63 patients
2. dosimetric findings obtained in the first 63 patients appear to confirm our predictions.
3. optimal patient accrual, with an acceptance rate of 96 % among patients who refused the initial recommendation for conventional six weeks of post-segmental mastectomy fractionated radiotherapy
4. divulgation of the NYU experience through publications and the formation of a School for Prone Partial Breast Irradiation (see appendix 1)

REPORTABLE OUTCOMES:

Since the award was received the study has been presented by the P.I. at the following international and national conferences (all CME approved):

- IV Madrid Breast Cancer Conference: changes in the treatment of breast cancer. Madrid, June 7-9, 2001

- Mayo Clinic Amelia Island Oncology Review Course
August 15-18, 2001

- Manhattan Breast Cancer Society, Invited Speaker
January 17, 2002

- V Madrid Breast Cancer Conference: changes in the treatment of breast cancer.
Madrid June 11-13, 2003

- American Society for Therapeutic Radiology and Oncology (ASTRO) 45th Annual Meeting, Salt Lake City, Utah, October 19-23, 2003

- Emerging Trends in Adjuvant Therapy of Breast Cancer: 2003 Symposium in New York, October 24-26, 2003

- Future of Breast Cancer Meeting, Bermuda Islands: July 22-25, 2004

- San Raffaele University, Milan, Italy. Grand Rounds Invited Speaker, December 20, 2004

- 4th International Conference of ISIORT (International Society of Intraoperative Radiation Therapy) InterContinental Hotel Miami, Florida, March 17-19, 2005

- Columbia University Grand Rounds Invited Speaker, March 3rd, 2005

-UCLA University Grand Rounds Invited Speaker, May 23, 2005

THE NYU SCHOOL FOR PRONE PARTIAL BREAST IRRADIATION

Trough the support of this IDEA grant the NYU team has influenced the current "paradigm shift" of breast radiotherapy. The technique developed at NYU was reported in the recent issue of Seminars in Radiation Oncology. Investigators from other academic institutions have visited us to learn the technique and because of the growing demand we have established

CONCLUSIONS:

The current trial has shown to be feasible and well tolerated. The encountered acceptance rate is 96% in the studied population and the accrual is close to the expected target (63/90).
Preliminary dosimetric findings encourage us to continue especially in view of the excellent tolerability of this approach. No one patient recurred so far. The study will continues in Stage 2 until at most 99 patients are entered.
Longer follow-up is required for efficacy, cosmesis and to assess the role of circulating TGF-β1 pre-treatment as a marker for post-treatment fibrosis.
The study continues as planned and approved.

REFERENCES:

1) Formenti SC, et al Radiology. 2002 Jan;222(1):171-8
2) Joszef G et al Medical Physics 27(5): 1005-10 2000

APPENDICE 1:

Copy of 4 manuscripts pertaining to the research of this IDEA grant.

1. Formenti SC, Truong MT, Goldberg JD, Mukhi V, Rosenstein B, Roses D, Shapiro R, Guth A, Dewyngaert JK. Prone accelerated partial breast irradiation after breast-conserving surgery: Preliminary clinical results and dose-volume histogram analysis. Int J Radiat Oncol Biol Phys. 2004 Oct 1;60(2):493-504.
2. Rosenstein BS, Lymberis SC, Formenti SC. Biologic comparison of partial breast irradiation protocols. Int J Radiat Oncol Biol Phys. 2004 Dec 1;60(5):1393-404.
3. Formenti SC. External-Beam Partial Breast Irradiation. Seminars in Radiation Oncology, 2005, Feb vol 15, (2).
4. Formenti SC, Lymberis SC, Rosenstein BS. In response to Dr. Morgan. Int J Radiat Oncol Biol Phys. 2005 Jul 1;62(3):943-4.

Copy of Slide Show of Prone Partial Breast Irradiation School.

Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 2, pp. 493–504, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.04.036

APPENDIX 1

CLINICAL INVESTIGATION **Breast**

PRONE ACCELERATED PARTIAL BREAST IRRADIATION AFTER BREAST-CONSERVING SURGERY: PRELIMINARY CLINICAL RESULTS AND DOSE–VOLUME HISTOGRAM ANALYSIS

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VANDANA MUKHI, M.A.,† BARRY ROSENSTEIN, PH.D.,* DANIEL ROSES, M.D.,‡
RICHARD SHAPIRO, M.D.,‡ AMBER GUTH, M.D.,‡ AND J. KEITH DEWYNGAERT, PH.D.*

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Purpose: To report the clinical and dose–volume histogram results of the first 47 patients accrued to a protocol of accelerated partial breast irradiation. Patients were treated in the prone position with three-dimensional conformal radiotherapy after breast-conserving surgery.

Methods and Materials: Postmenopausal women with Stage T1N0 breast cancer were eligible only after they had first refused to undergo 6 weeks of standard radiotherapy. Planning CT in the prone position was performed on a dedicated table. The postoperative cavity was defined as the clinical target volume, with a 1.5-cm margin added to determine the planning target volume. A total dose of 30 Gy at 6 Gy/fraction was delivered in five fractions within 10 days.

Results: The median age of the patients was 67.5 years (range, 51–88 years). The median tumor diameter was 9 mm (range, 1.3–19 mm). In all patients, the prescribed dose encompassed the planning target volume. The mean volume of the ipsilateral breast receiving 100% of the prescription dose was 26% (range, 10–45%), and the mean volume contained within the 50% isodose surface was 47% (range, 23–75%). The lung and heart were spared by treating in the prone position. Acute toxicity was modest, limited mainly to Grade 1-2 erythema. With a median follow-up of 18 months, only Grade 1 late toxicity occurred, and no patient developed local recurrence.

Conclusion: These data suggest that this approach is well tolerated, with only mild acute side effects and sparing of the heart and lung. © 2004 Elsevier Inc.

Hypofractionation, Prone, Partial breast irradiation, Early-stage breast cancer.

INTRODUCTION

The widespread use of screening mammography during the past three decades has generated a new patient population, consisting of postmenopausal women with mammographically detected, nonpalpable, early-stage, invasive breast cancer. These tumors are often T1N0M0, Stage I, estrogen receptor-positive tumors, ideal for breast-conserving therapy (BCT) (1). A more user-friendly regimen than the standard 5–7 weeks of postoperative radiotherapy (RT) has recently become an area of intense research, because in certain patient populations, including the elderly and patients living remote from radiation facilities, BCT and/or postoperative RT appear to be underutilized (2–6). Because no patient subgroup has had a sufficiently low risk of in-breast recurrence to avoid whole breast RT routinely after segmental mastectomy (7), a shorter RT regimen could minimize inconvenience and improve the use of BCT.

The results of five prospective randomized trials testing breast-preserving surgery with or without adjuvant RT have suggested that most failures occur at the tumor bed, thus questioning the necessity for routinely irradiating the whole breast (7–11). The ipsilateral breast tissue outside the tumor bed appears to carry a risk of recurrence or new breast cancer development that is equivalent to that of the contralateral breast (0.5–1% annually), which is routinely not irradiated. Limiting RT to a smaller target than the whole breast has the potential to reduce radiation-induced morbidity. The main advantage of partial breast RT is the opportunity to increase the dose per fraction to accelerate treatment by limiting the volume of treated normal tissue.

Although several groups have focused on brachytherapy

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Accepted at the 45th ASTRO Annual Meeting as a poster presentation.

Supported by Department of Defense Grant DAMD17-01-1-0345 and NYU Cancer Institute Core Grant.

Received Jan 16, 2004, and in revised form Apr 13, 2004. Accepted for publication Apr 13, 2004.

Table 1. Study schema for Stage I breast cancer postmenopausal, nonpalpable tumors, after segmental mastectomy

	Informed consent	Blood collection for TGF-β
	CT planning in prone position, determination of tumor bed and ipsilateral breast tissue	
Days 1–10	Conformal tumor bed radiotherapy 6 Gy × 5 fractions in 2 wk Days 1, 3, 5, 8, 10 (total dose, 30 Gy)	
Day 10	Last day of treatment	Blood collection for TGF-β

as the technique to deliver accelerated partial breast irradiation (APBI) (12–16), in the early 1990s we started investigating an external beam RT approach for partial breast treatment (17). Prone positioning of the patient rapidly emerged as the best technique, because it minimizes movement of the target breast tissue during breathing and achieves maximal sparing of normal heart and lung tissue. A pilot trial was conducted at the University of Southern California (USC)/Kenneth Norris Jr. Cancer Center to test the feasibility of a short course of hypofractionated conformal RT to the tumor bed in the prone position as part of a breast conservation protocol in postmenopausal patients with nonpalpable Stage pT1N0 breast cancer. A radiosurgery-like technique of multiple noncoplanar fields was tested, and 10 patients were randomly assigned to five fractions of 5, 5.5, or 6 Gy, on the basis of radiobiologic linear-quadratic modeling. These doses were chosen in view of their radiobiologic equivalence to 50 Gy in 25 fractions when an α/β value of 4 is used for the prediction of tumor control (18–20). Local control and cosmetic results were excellent at a minimal follow-up of 36 months (21).

In 2000, funded by an IDEA grant from the Department of Defense, a Phase I-II trial was initiated in the Department of Radiation Oncology at New York University to determine the feasibility and efficacy of prone, partial breast conformal RT to the tumor bed in postmenopausal women with T1N0M0 breast cancer who had undergone segmental mastectomy and had refused standard postoperative whole breast RT.

METHODS AND MATERIALS

On the basis of the data originated from the initial pilot study (21), a regimen of 30 Gy delivered in five fractions within 10 days was chosen for this study. In addition, because the biologically effective dose (BED) (18) calculations predicted fibrosis as the dose-limiting toxicity, the study included blood collection for measurement of transforming growth factor-β1 levels in pretreatment plasma, as a marker for the development of post-RT fibrosis (Table 1) (22).

Justification of radiobiologic dose and fractionation

The linear-quadratic model and the BED equation, $BED = (nd)(1+d/\alpha/\beta)$, derived from this model (18, 23), were used to calculate the appropriate total dose and fraction size for the hypofractionated protocol. In this formula, n is the number of fractions and d is the dose/fraction. This equation was used to calculate the BEDs for early and late responses and tumor control for the hypofractionated schedule (five fractions of 6 Gy delivered within 10 days) and two standard schedules (25 fractions of 2 Gy within 5 weeks, considered the standard treatment without a boost [24] and 30 fractions of 2 Gy within 6 weeks—46 Gy to the entire index breast plus a boost of 14 Gy to the tumor cavity, considered the standard treatment with a boost). These calculations assumed that full repair takes place during the ≥24-h interval between fractions. Table 2 lists the BEDs for tumor control, in addition to the early responses, erythema and desquamation, and late responses, telangiectasia and fibrosis. The BEDs for the normal tissue acute responses were generally lower for the hypofractionated schedule than for the standard treatment regimens, indicating the risk of radiation-induced complications should be lower in the hypofractionated schedule (Table 2).

For tumor control, if we used an α/β value of 10 Gy, the typical value for many tumors (25, 26), in this calculation, the BED computed for the hypofractionated schedule would be substantially lower than that for the standard treatments.

Table 2. Biologically effective doses

	α/β (Gy)	Standard (60 Gy/30 Fx)	Standard (50 Gy/25 Fx)	Hypofractionated (30 Gy/5 Fx)
Erythema	8	75 Gy_8	63 Gy_8	53 Gy_8
Desquamation	11	71 Gy_{11}	59 Gy_{11}	46 Gy_{11}
Telangiectasia	4	90 Gy_4	75 Gy_4	75 Gy_4
Fibrosis	2	120 Gy_2	100 Gy_2	120 Gy_2
Tumor	4	90 Gy_4	75 Gy_4	75 Gy_4
Tumor*	4	86 Gy_4	72 Gy_4	75 Gy_4
Tumor	10	72 Gy_{10}	60 Gy_{10}	48 Gy_{10}
Tumor*	10	68 Gy_{10}	57 Gy_{10}	48 Gy_{10}

* Taking into account cell proliferation during course of treatment.

However, if the α/β value is set at 4 Gy, as suggested by experiments involving irradiation of human breast cancer cell lines (18–20), the BED calculated and, therefore, the likelihood of tumor control associated with the hypofractionated schedule, would be identical to that of the standard treatment without a boost. In addition, because the hypofractionated regimen also represents an accelerated protocol in which the total dose is delivered in only 10 days, less tumor proliferation is expected to take place compared with that occurring during the standard treatment. By taking these factors into account, the difference between the BEDs for the two schedules is reduced (Table 2).

Study population

Study eligibility was limited to postmenopausal women with newly diagnosed, nonpalpable, mammographically detected, invasive breast cancer. Menopause was defined as at least 2 years without menstrual periods. In patients who had undergone prior hysterectomy, follicle-stimulating hormone levels were measured for confirmation of postmenopausal status. Only those with pT1, pN0 or sentinel node negative, or N0 clinically if the tumor was <1 cm in size, were eligible. In addition, patients were required to have undergone segmental mastectomy or reexcision with negative surgical margins (at least 5 mm) and to have estrogen and/or progesterone receptor-positive tumors. Antihormonal therapy (tamoxifen or anastrozole) was prescribed in all cases.

The exclusion criteria were previous RT to the ipsilateral breast, extensive intraductal component in the pathologic specimen, a diagnosis of multifocal breast cancer, or the inability to provide informed consent as assessed by the Principal Investigator. All eligible women who were referred to the Radiation Oncology Department at the New York University School of Medicine for RT after breast-conserving surgery for breast cancer were first offered standard conventional 6-week RT. Only women who declined standard RT were given the opportunity to participate in the current protocol by providing informed consent. The New York University institutional review board and the institutional review board of the Department of Defense reviewed and approved all aspects of the study.

Toxicity was assessed every week during treatment. Patients were followed monthly with physical examination for the first 90 days, every 3 months for the first year, every 6 months for the next 4 years, and yearly thereafter to evaluate their status with respect to recurrence, long-term toxicity, and cosmesis. Toxicity was evaluated at each visit according to the Radiation Therapy Oncology Group toxicity scoring criteria. Cosmesis was recorded by the patient at baseline (before RT started) and then every 6 months.

Simulation and treatment planning

Patients were placed in the prone position on a dedicated treatment table for CT planning and treatment (Figs. 1–3). The table has an aperture to allow the breast to fall by gravity away from the chest wall (17). Patient positioning on the table was established by two lateral lasers and one overhead laser. Noncontrast CT images were acquired at 3.75-mm-thick intervals from the level of the mandible to below the diaphragm using a GE Light speed helical CT scanner. CT images were transferred to a Varian Eclipse treatment planning system (Varian Cadplan, Varian Medical Systems, Palo Alto, CA). The surgical cavity, identified at CT as the area of architectural distortion in the breast tissue, defined the clinical target volume (CTV) (Fig. 4). When necessary, information obtained from the surgical report, mammography findings, and other available imaging test results were also incorporated. Although not intentionally included by the CTV, the surgical incision was outlined by a wire placed over the incision before CT scanning.

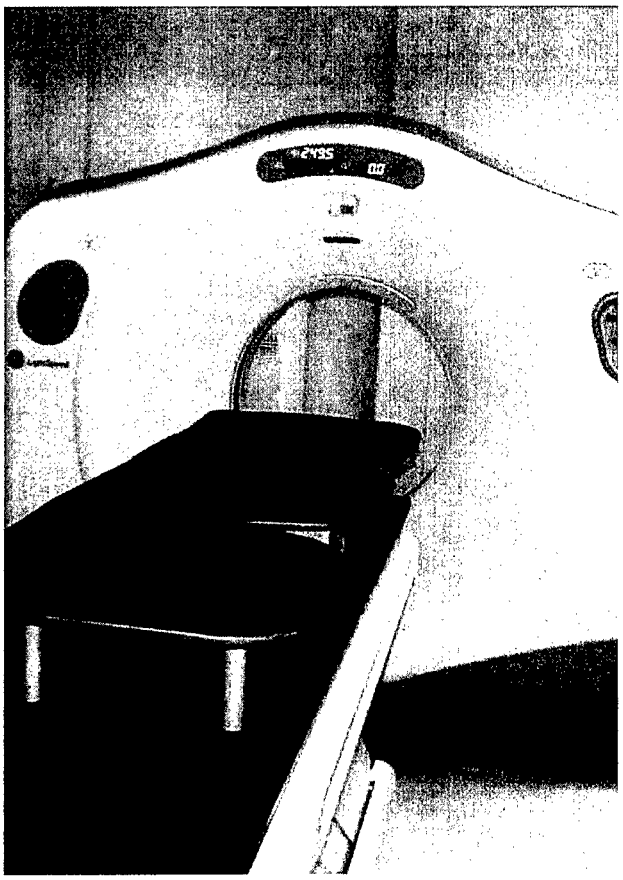


Fig. 1. Computed tomography simulator and prone breast table.

Adding a 1.5–2-cm margin to the CTV created the planning target volume (PTV). After uniform expansion, the PTV was limited anteriorly by the skin and posteriorly by the chest wall. An additional 7-mm margin was added to the PTV to the field edge to account for beam penumbra, for a total margin of 2.2–2.7 cm. The ipsilateral lung and heart were outlined. The normal ipsilateral breast tissue volume was defined by applying radiopaque wires in the supine position at the site of the medial, lateral, inferior, and superior borders of the classic opposite tangent breast fields to define the volume that would have been treated by classic whole breast tangents in the supine position.

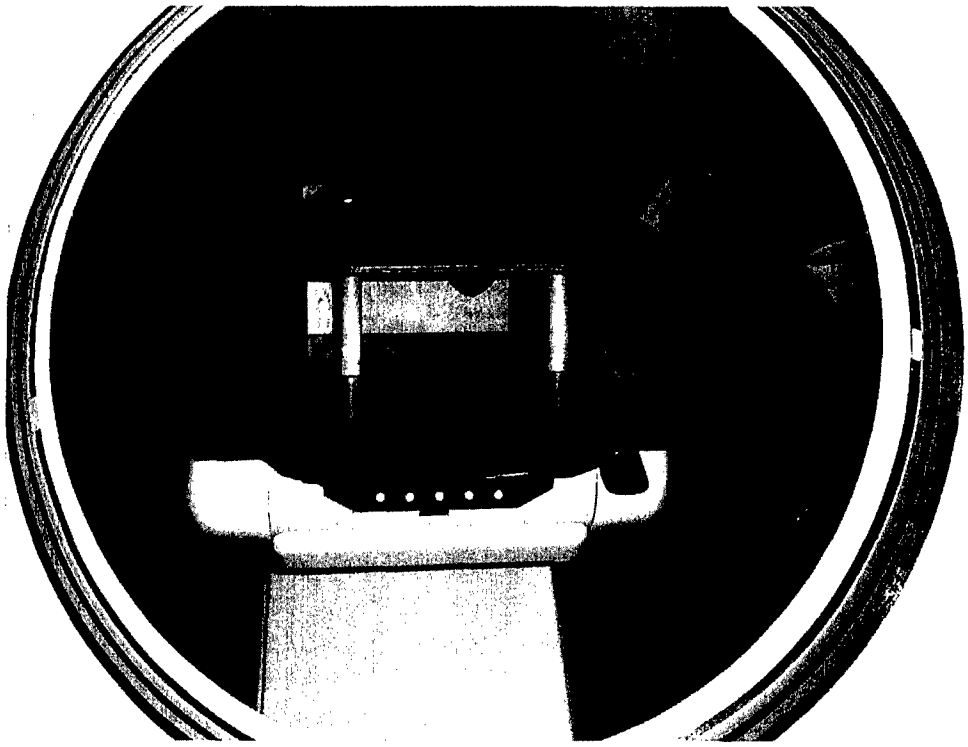


Fig. 2. Positioning and setup. Patient is positioned prone on a dedicated table that allows the target breast tissue to fall freely through the opening.

Dose–volume constraint guidelines

Treatment planning was performed using the CT-defined volumes, most often through an opposed pair of mini-tangents. When required to increase dose distribution homogeneity, wedges were used. The isocenter was located approximately 5–7 cm from the midline along an axis passing through the center of the PTV. The dose was normalized to 100% at the isocenter before choosing an

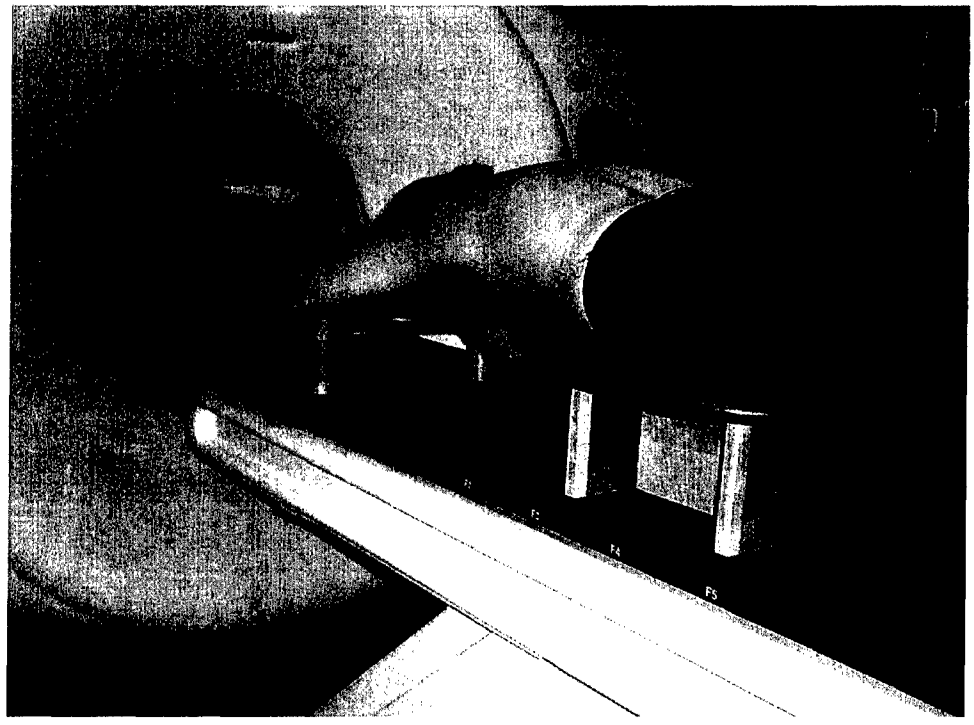


Fig. 3. Patient undergoing computed tomography acquisition of images.

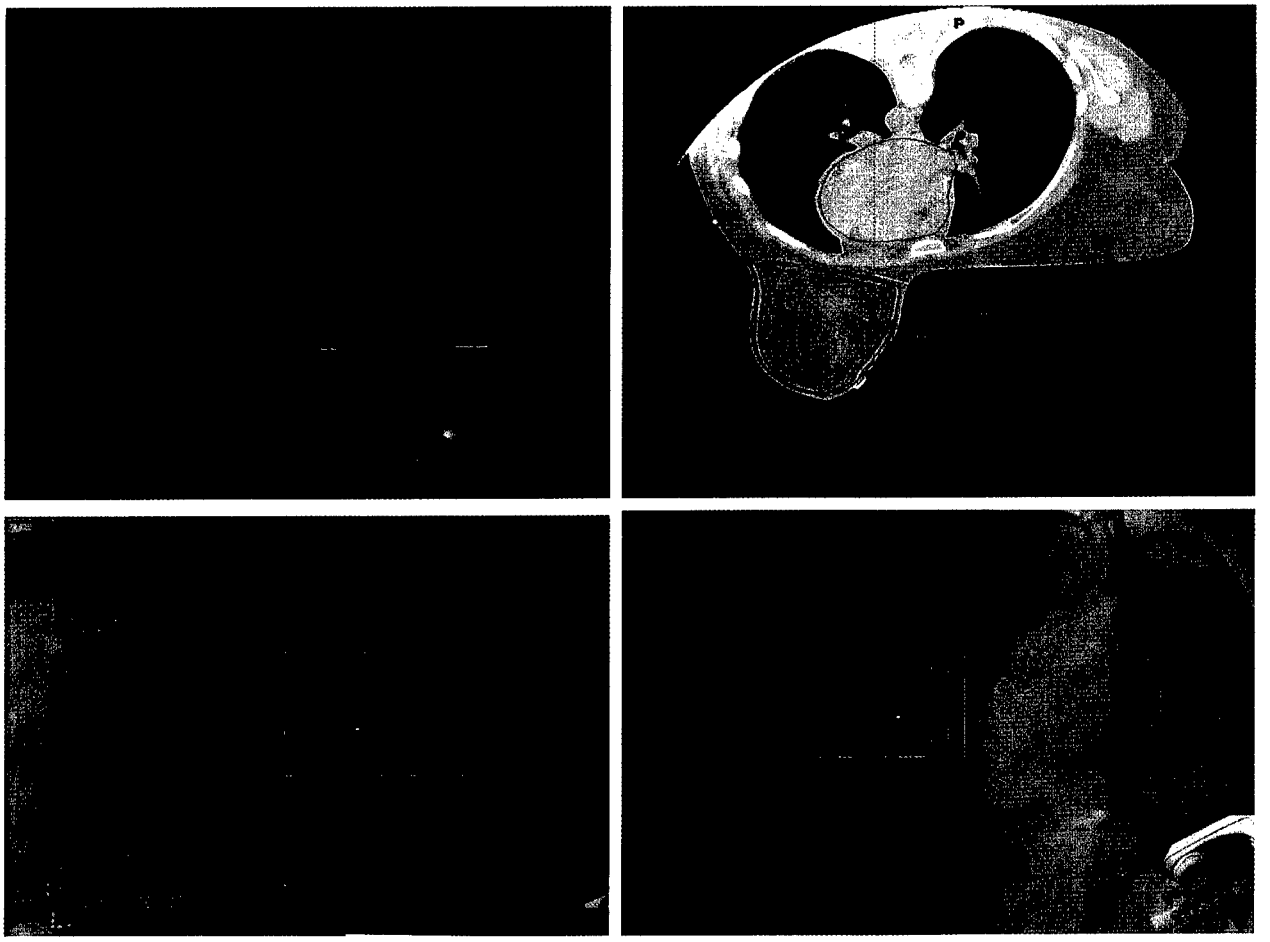


Fig. 4. (Upper) Example of relationship of tumor bed to planning target volume (PTV) demonstrated; tumor bed in red wash, PTV in blue, heart in pink, and lung in light green. PTV represents a 1.5-cm margin on tumor bed. (Lower) Digital reconstructed radiographs, right anterior oblique and left posterior oblique portals for left-sided breast cancer.

isodose surface that encompassed the PTV, typically 95%. Dose inhomogeneity was maintained at <110%.

Additional normal tissue dose guidelines included limiting 50% of the ipsilateral breast volume to <50% of the prescribed dose. In addition, the volume of heart and lung included in the treatment fields was expected to be <10%. Field arrangements were designed to avoid the contralateral breast and ipsilateral lung and heart tissue completely (Fig. 4). The dose fractionation schedule was 30 Gy delivered in five fractions of 6 Gy to the 95% isodose surface, given within 10 days (Monday, Wednesday, Friday, Monday, Wednesday).

Target positioning verification

Treatment room lasers were used to verify consistent positioning of the patient on the table. Daily setup reproducibility was ensured by leveling marks on the torso and triangulation marks placed on the back, ipsilateral side, and breast tissue (Fig. 5). The setup was designed to identify a plane orthogonal to the table that also crossed the tumor cavity. Before each fraction, portal films of each field verified treatment positioning. Accepted variance was limited to 5 mm from the isocenter position indicated on the digitally reconstructed radiographs (Fig. 6).

Statistical analysis

An optimal two-stage Simon design was used for this Phase II trial (27). It is based on testing the null hypothesis that the 3-year local recurrence rate is ≥9% vs. the alternative that the 3-year local recurrence rate is ≤3% (α 0.05; power of 0.80). The study was designed to enroll 31 patients in the first stage and up to 99 patients during the entire trial. If two or fewer local recurrences developed in the first 31 patients who completed at least 1 year of follow-up, accrual would continue up to completion of the second stage. If five or more local recurrences were observed at any point, the trial would be stopped. The trial will be terminated when at most 99 patients have been entered and followed for at least 1 year. Any ipsilateral breast local recurrence, whether a true local recurrence (within the radiation field) or breast local recurrence outside the field, was the main study endpoint (including both isolated recurrence and concomitant with distant disease).

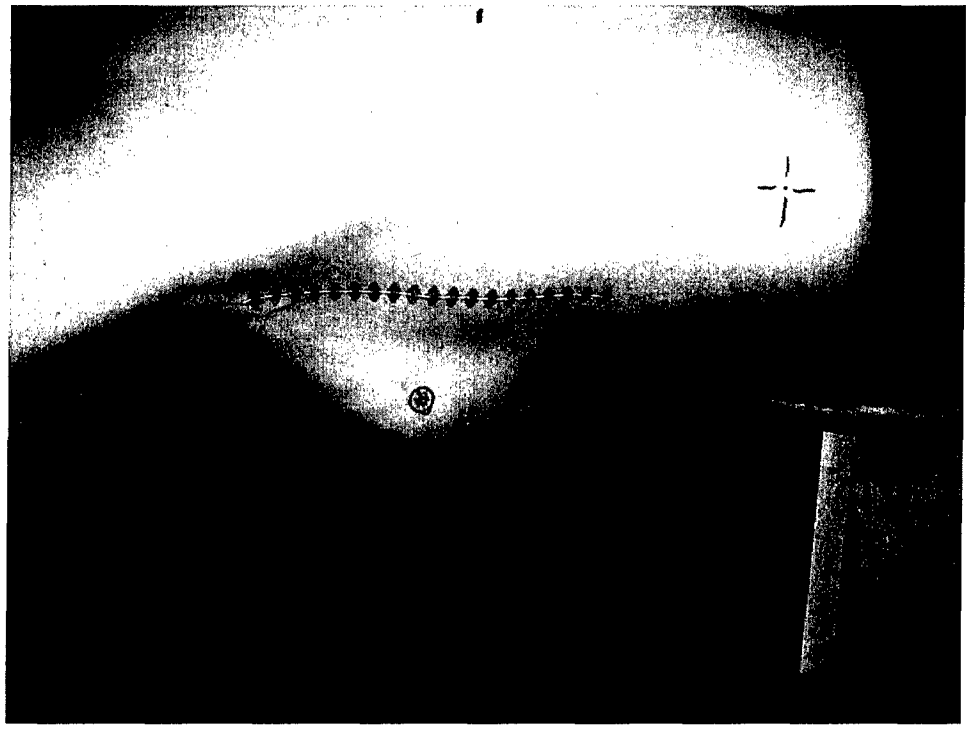


Fig. 5. Target position verification by triangulation marks placed carefully on back, ipsilateral side, and breast.

RESULTS

Clinical results

Between June 2000 and December 2003, 50 patients were enrolled in the study. A summary of the baseline patient and tumor characteristics is provided in Tables 3 and 4, respectively, and includes the mean, median, quartiles, and range for continuous variables and frequency distributions for categorical variables. Of the 50 screened patients, 47 entered the treatment phase and 46 completed treatment. Three patients were lost to follow-up before initiating any treatment, and 1 patient discontinued treatment after two fractions for personal reasons. She reported no acute toxicities.

The median length of follow-up was 18 months (range, 0.3–40.3 months). Of the 46 patients, 30 were followed for $\geq$1 year since the start of treatment without any local recurrences, and the study continues to accrue patients. The follow-up distribution is shown in Table 5.

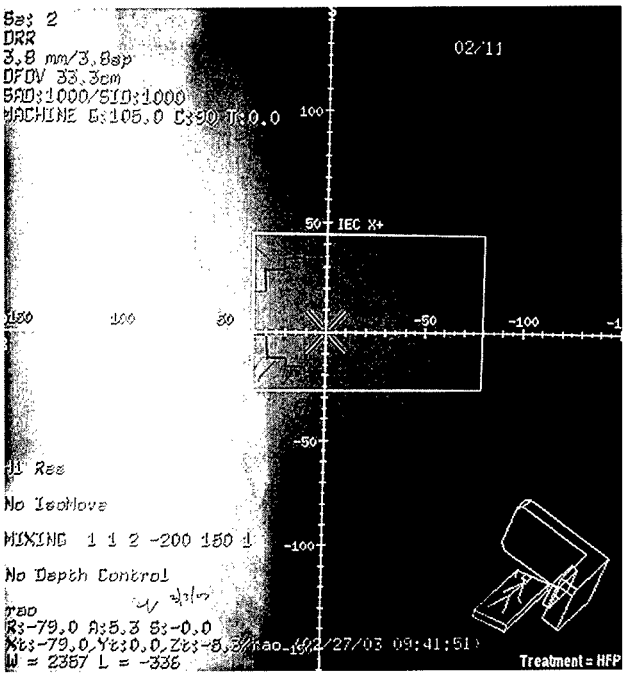
The most common acute toxicity noted was Grade 1-2 erythema, observed in 28 patients (60% of patients treated; Table 6). A preliminary assessment of late toxicity has indicated that these were primarily Grade 1 (Table 6). A total of 21 late toxicities have occurred in 14 patients. Eight patients had Grade 1 induration before RT, related to the surgery. Cosmetic results were rated as "good/excellent" in 7 patients with 6–12 months of follow-up, 3 patients with 12.1–18 months of follow-up, 5 patients with 18.1–24 months of follow-up, 12 patients with >2 years of follow-up, and 5 patients with >3 years of follow-up. In 2 patients, the cosmetic results were rated as "fair" at 12 and 18 months of follow-up. The remaining patients have had <6 months of follow-up. In none of the patients was the post-RT score worse than at the baseline postoperative assessment.

At last follow-up, no patient had developed local recurrence. One patient developed metastatic squamous cell carcinoma of the lung with mediastinal, paraspinal, and osseous metastases 2 months after RT completion. No evidence of malignancy could be found at review of the chest X-ray obtained before undergoing segmental mastectomy. Her condition rapidly deteriorated because of metastatic lung cancer and she died 3 months after completion of the protocol treatment.

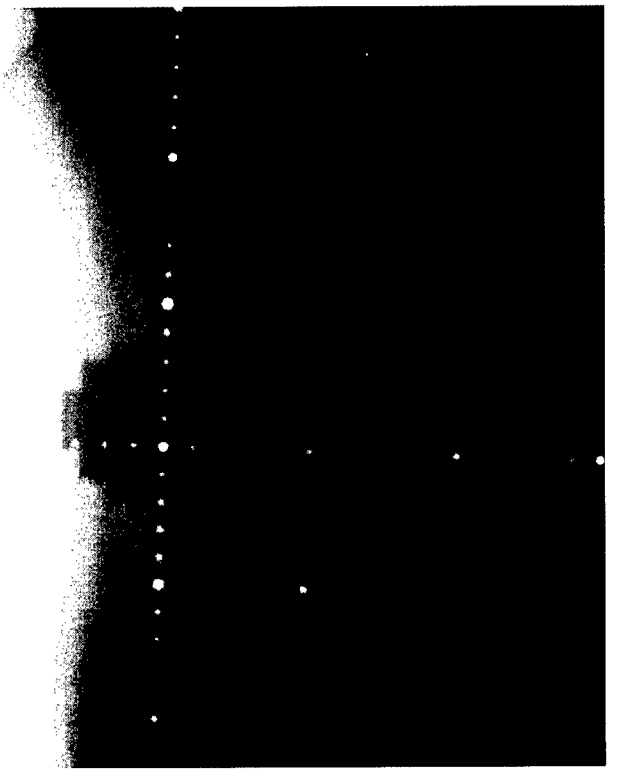
Physics results

Of the 47 patients, 43 were treated in the prone position. Four patients were treated in the supine position (as accepted protocol deviations by the principal investigator). Of the 4 patients, 2 could not tolerate prone positioning because of a preexisting physical disability (hemiparesis due to a previous stroke in 1 and multiple sclerosis in another 1). The third patient could not be treated in the prone position without treating the arm and contralateral breast because of severe kyphosis, secondary to osteoporosis. In the fourth patient, the tumor bed was located lateral and superior in tail of Spence, and it was better treated in the supine position.

The predominant technique for treatment was a pair of parallel-opposed mini-tangents. This arrangement provided a simplified treatment setup and ensured good coverage, given the constraints imposed by the PTV and its relationship to the table (Fig. 4).



(a)



(b)

Fig. 6. (a) Right anterior oblique digital reconstructed radiograph. (b) Right anterior oblique port film.

Dosimetric findings

The dosimetric results are summarized in Tables 7 and 8. The mean and median size of the surgical cavity (CTV) at CT acquisition was 52 cm^3 and 34 cm^3 (range, 7–379 cm^3), respectively. The mean and median volume of the PTV was 228 cm^3 and 192 cm^3 (range, 57–1118 cm^3), respectively. The mean and median volume of the ipsilateral breast were 1102 cm^3 and 1006 cm^3, respectively (range, 258–3468 cm^3). The mean and median coverage of the PTV by the 30 Gy isodose surface were both 100%.

Dose–volume histograms of the ipsilateral breast volume (Fig. 7), lung and heart were generated. The mean and

Table 3. Baseline patient characteristics (n = 47)

	Patients (n)
Race	
Black	1 (2.1)
Hispanic	2 (4.3)
White	44 (93.6)
Performance status at screening	
0	19 (40.4)
1	24 (51.1)
2	1 (2.1)
Unknown	3 (6.4)
Breast side	
Left	27 (57.5)
Right	20 (42.6)
Hormonal replacement therapy	
Current	4 (8.5)
Past	15 (31.9)
None	27 (57.5)
Unknown	1 (2.1)
Tumor estrogen receptor status	
Negative	1 (2.1)
Positive	46 (97.9)
Tumor progesterone receptor status	
Negative	13 (27.7)
Positive	34 (72.3)
Tumor Her2-neu status by IHC	
0	31 (65.9)
+	7 (14.9)
++	4 (8.5)
+++	3 (6.4)
Unknown	2 (4.3)

Data in parentheses are percentages.

Table 5. Follow-up distribution from start of treatment to last observation

Follow-up (mo)	Patients (n)
0–6	11 (23.4)
6–12	6 (12.8)
12–18	7 (14.8)
18–24	4 (8.5)
24–30	5 (10.6)
30–36	6 (12.8)
36–42	8 (17.1)
Total	47 (100.0)

Data in parentheses are percentages.

Table 6. Acute and late toxicity

Toxicity	Worst grade	Toxicities (n)
Acute (n = 28/47)		
Breast swelling	1	1 (2.7)
Desquamation	1	2 (5.4)
Erythema	1	21 (56.7)
	2	5 (13.5)
Late (n = 14/47)		
Erythema	1	2 (9.5)
Fibrosis	1	2 (9.5)
Hyperpigmentation	1	3 (14.4)
Induration	1	8 (38.1)
Telangiectasia	1	5 (23.8)
Other	1	1 (4.8)

Data in parentheses are percentages.

median volume of the ipsilateral breast receiving 100% of the prescription dose was 26% and 27% (range, 10–45%), respectively. The mean and median volume receiving 50% of the prescription dose was 47% and 46% (range, 23–75%), respectively. We found heterogeneity in the dose–volume histogram based on the position of the original tumor bed and the size of the breast. In 25% of patients (12 of 47), to successfully treat the PTV, >50% of the ipsilateral breast volume received >50% of the prescription dose.

Dose to heart and lung

The mean percentage of lung volume receiving 20, 10, and 5 Gy was 0% (range, 0–4%, 0–6%, and 0–10% respectively) for all. The mean percentage of heart volume receiving 20, 10, and 5 Gy was also 0% (Table 8). These doses were less than what has been reported using partial breast irradiation in the supine position (28). Prone positioning allowed sparing of these critical structures by allowing the breast tissue to fall away from the chest wall and minimizing breast movement secondary to the respiratory excursion that commonly occurs in the supine position. In the 4 patients treated supine in this study, the median dose to the lung receiving 20, 10, and 5 Gy was 2%, 4%, and 6%, respectively.

DISCUSSION

The current study represents the largest reported experience of three-dimensional conformal external beam RT for APBI as part of BCT. With the limitation of a short median follow-up of only 18 months, these results support the safety and feasibility of the regimen.

Several differences characterize this approach compared

Table 4. Baseline tumor characteristics (n = 47)

Variable	Mean	Q3	Median	Q1	Range
Age (y)	68	77	68	61	52–88
Tumor size (mm)	9.6	13.0	9.0	7.0	1.3–19
Follow-up (mo)	19.0	32.5	16.7	6.2	0.3–40.3

Abbreviations: Q3 = third quartile; Q1 = first quartile.

Table 7. Dosimetric findings: CTV, PTV, and IBV

Dosimetric characteristics	Mean value	Median value	Range
IBV (cm^3)	1102	1006	258–3468
CTV (cm^3)	52	34	7–379
PTV (cm^3)	228	192	57–1118
Maximal dose (% of PD)	110	108	105–117
PTV coverage by 95% isodose surface (%)	100	100	—
Ispilateral breast coverage (% IBV encompassed by % of PD)			
100% of PD	26	27	10–45
75% of PD	41	40	20–68
50% of PD	47	46	23–75
25% of PD	53	53	27–82
CTV/IBV (%)	5	4	1–22
PTV/IBV (%)	22	20	10–55
CTV/PTV (%)	20	20	6–46

Abbreviations: CTV = clinical target volume (tumor bed); PTV = planning target volume; IBV = ipsilateral breast volume; PD = prescribed dose.

Table 8. Dosimetric findings of normal tissue: heart and lung

Dosimetric characteristics	Mean (%)	Median (%)	Range (%)
Ipsilateral lung			
V 20 Gy	0	0	0–4
V 10 Gy	1	0	0–6
V 5 Gy	2	0	0–10
Heart			
V 5 Gy	0	0	0

Abbreviation: V = percentage of volume receiving specified dose.

Values rounded to nearest whole number.

with those reported by other groups studying partial breast RT with an external beam technique. First, the patients in this study received treatment in the prone position (21). The advantages of a prone technique are manifold. Prone positioning considerably reduces the breast tissue motion secondary to both cardiac systole and respiration (29), limiting the excursion of the chest wall to <5 mm (17). With the triangulation technique we developed for positioning, the breast tissue remains a predictably fixed target. In addition, prone positioning allows for exclusion of lung and heart tissue from the treatment fields (30). This is particularly relevant in view of the growing evidence of the late morbidities these organs derive from breast irradiation in the supine position (31–35). Moreover, in women with pendulous and/or large breasts, treatment in the prone position allows the breast tissue to fall away from the chest wall preventing skin desquamation along the inframammary fold, a common occurrence when treated supine. Finally, based on BED modeling, instead of the approach (twice daily during 5 days) used by the investigators at Beaumont Hospital (28, 36), the treatment described consisted of five fractions within 10 days, a schedule that was easy to adhere to, even for elderly patients.

Compared with partial breast RT using brachytherapy, the advantages of prone external beam APBI consist of its noninvasive nature, the simplicity of the field arrangements and ease of patient setup. Potentially, any RT facility equipped with CT planning and a linear accelerator could adopt this approach.

However, many challenges remain associated with this area of breast cancer radiation research. For example, the exact identification of the target remains to be defined. Placement of clips has been suggested to facilitate the radiographic identification of the cavity; however, signifi-

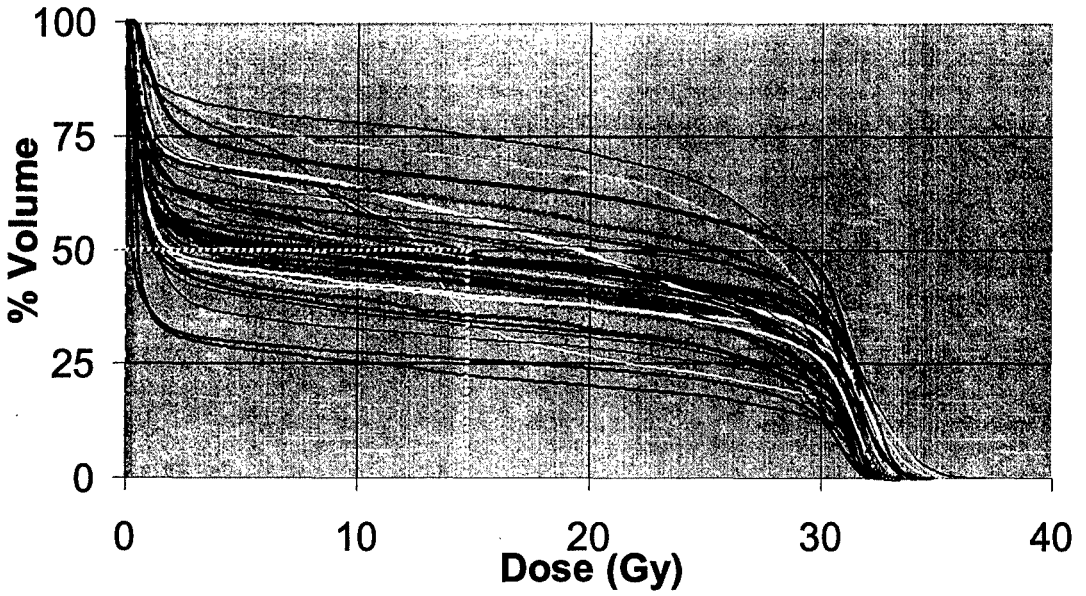


Fig. 7. Dose–volume histogram of ipsilateral breast of 47 patients.

cant clip migration has been reported, particularly after breast biopsy procedures, making reliance on the technique questionable (37). In the current series of patients, the cavity was identified by CT planning. Owing to our selection criteria, none of the patients had undergone chemotherapy, making it possible to plan and start RT close to the time of surgery, when the postexcision cavity could more easily be identified (Fig. 4). Although we found no correlation with the interval between surgery and the date of CT acquisition of the CTV, it could be possible that with increasing time after surgery, the accuracy of CTV definition by CT might diminish. In the future, if APBI is revealed to be equivalent to standard RT, the argument of delivering it before systemic treatment could be made, in view of its brief course and the optimal visualization of the tumor bed soon after surgery.

The best dose/fractionation regimen for APBI also remains to be determined, in terms of both ensuring optimal tumor control and cosmetic outcome. With regard to the latter, even if it is not predicted by the BED modeling, hypofractionated regimens may carry some risk of late effects, such as breast fibrosis and telangiectasia. Currently, no predictive markers are routinely available to determine which patients will develop radiation-induced late toxicity. In a study by Li *et al.* (22), a statistically significant correlation between the pretreatment plasma levels of transforming growth factor-β1 (a multifunctional cytokine implicated in tissue fibrosis) was found in patients treated with BCT who developed severe post-RT fibrosis. The regimen used consisted of 40 Gy in 15 fractions to the whole breast. Other studies have revealed that specific polymorphisms of the transforming growth factor-β1 promoter gene might be associated with the development of severe fibrosis. Quarmby *et al.* (38) reported that patients with the −509TT or +869CC genotypes were 7–15 times more likely to develop severe fibrosis. Future genetic studies might enable the identification of a panel of polymorphic sites associated with fibrosis that could make it possible to prospectively detect "fibrosis-prone" individuals. In the current study, pretreatment blood samples are prospectively collected to test this hypothesis.

A more serious concern is the risk of underdosing the tumor bed. In an associated paper, we have discussed in depth the results obtained by radiobiologic modeling of most currently used partial breast irradiation protocols. All regimens currently used result in inferior BED values for tumor effects compared with those achieved by 60 Gy in 30 fractions during 6 weeks. For the current regimen, the dose chosen was derived by matching the same BED values (75 Gy_2) for tumor control of a standard regimen of 50 Gy in 25 fractions. When the protocol was originally designed, controversy existed regarding the value of adding a boost after 50 Gy to the whole breast, the regimen used in the RT arm of National Surgical Adjuvant Breast and Bowel Project clinical trial B-06. For instance, in a contemporary publication, Hayman *et al.* (39) had addressed the cost-effectiveness of an electron boost and, based on the evidence available at that time, concluded that its ratio in quality-adjusted life years was "well above the commonly cited threshold for cost-effective care." However, in view of the evidence subsequently generated by the European Organization for Research and Treatment of Cancer trial of a dose–response relation at the tumor bed, the currently used experimental regimen could be inadequate to ensure optimal local control in a nonselected cohort of women treated by BCT (40). Whether the hypofractionated regimen (30 Gy in 5 fractions within 10 days) will be revealed as adequate in ensuring tumor control in the carefully selected population studied in this trial warrants long-term follow-up.

The issue of optimal patients selection also remains unanswered: does a specific subset of women exist for whom partial breast RT is equivalent to whole breast RT? Controversy exists with regard to eligibility for partial breast RT studies. Contrary to the results of Vicini *et al.* (41), who reported a promising 1% local recurrence rate at a median follow-up of 65 months after partial breast brachytherapy, a recent report from another group had a 60-month actuarial rate of ipsilateral recurrence of 16.2% (42). Also, four of the six in-breast recurrences occurred outside the lumpectomy site, even though each of the women with recurrence had originally had a mammographically detected T1 primary (42). We deliberately focused our study on the rapidly growing subset of breast cancer patients, postmenopausal women with mammographically detected tumors, a population in which 96% of the detected breast cancers are T1 lesions (43, 44). Long-term results from the current study will provide important preliminary results on whether a more user-friendly, cost-effective regimen can be safely offered to this population of patients with generally indolent breast cancers.

Finally, characteristic of the current study is that eligible patients also need to have refused to undergo the standard 6-week RT regimen to be offered the current protocol. This approach reflects our bias regarding the ethics of studying a potentially "lesser" treatment in a setting in which the standard therapy has resulted in exceptionally high success rates. Thus, two other important measures of caution were taken. First, eligibility is limited to postmenopausal women with a very low risk of ipsilateral in-breast recurrence, including the requirement for estrogen receptor positivity and antiestrogen treatment and, second, a Stage 2 Simon statistical design with early stopping rules, based on a 5% actuarial recurrence rate at 5 years, was chosen to minimize the risk to the patients who have elected to participate in the protocol.

In view of these results and of the many potential advantages, including increasing compliance to RT, thereby increasing the rate of breast preservation treatment, reducing adjacent normal tissue morbidity, and reducing the cost of postoperative RT (5 vs. 30 treatments), we are continuing the planned accrual of 99 patients to this trial.

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APPENDIX 2

ELSEVIER

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CLINICAL INVESTIGATION **Breast**

BIOLOGIC COMPARISON OF PARTIAL BREAST IRRADIATION PROTOCOLS

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Purpose: To analyze the dose/fractionation schedules currently used in ongoing clinical trials of partial breast irradiation (PBI) by comparing their biologically effective dose (BED) values to those of three standard whole breast protocols commonly used after segmental mastectomy in the treatment of breast cancer.

Methods and Materials: The BED equation derived from the linear-quadratic model for radiation-induced cell killing was used to calculate the BEDs for three commonly used whole breast radiotherapy regimens, in addition to a variety of external beam radiotherapy, as well as high-dose-rate and low-dose-rate brachytherapy, PBI protocols.

Results: The BED values of most PBI protocols resulted in tumor control BEDs roughly equivalent to a 50-Gy standard treatment, but consistently lower than the BEDs for regimens in which the tumor bed receives a total dose of either 60 Gy or 66 Gy. The BED values calculated for the acute radiation responses of erythema and desquamation were nearly all lower for the PBI schedules, and the late-response BEDs for most PBI regimens were in a similar range to the BEDs for the standard treatments.

Conclusion: Biologically effective dose modeling raises the concern that inadequate doses might be delivered by PBI to ensure optimal in-field tumor control. © 2004 Elsevier Inc.

Biologically effective dose, Breast cancer, Partial breast irradiation.

INTRODUCTION

The possibility of completing the course of postsegmental mastectomy radiotherapy (RT) in a smaller number of treatments within a shorter period is very appealing to breast cancer patients. If a shorter regimen proves equivalent to standard treatment, it could represent important progress in terms of cost-effectiveness for RT. Furthermore, the implementation of a breast cancer radiation protocol that is less cumbersome may help to address the logistical problems faced by many patients, particularly the elderly or those who live distant from a RT facility. These difficulties cause many patients who are candidates for breast conserving therapy either to select mastectomy or, worse, to simply forgo the RT portion of breast conserving therapy (1–3).

One method to accomplish this aim was attempted in the 1970s in several countries, where breast cancer patients received postmastectomy RT to the chest wall and draining nodes involving the use of larger-than-standard (1.8–2 Gy) fraction sizes or hypofractionation. For example, in one series, postmastectomy breast cancer patients were given 12 fractions to either a maximal absorbed dose of 51.4 Gy or a minimal target dose of 36.6 Gy specified at the level of the mid-axilla (4, 5). Many of the patients treated with these hypofractionated protocols subsequently developed chronic radiation injury, primarily fibrosis (4, 5). This discouraging experience rendered radiation oncologists hesitant to reexplore the use of large-dose fractions in the treatment of breast cancer.

It was only with the recent recognition of the common topographic pattern of local recurrence after segmental mastectomy that it became reasonable to question whether it is always necessary to irradiate the entire breast (6–10). The results from five prospective randomized trials are available to understand this issue better (6–9, 11). For instance, in the National Surgical Adjuvant Breast Project (NSABP)-06 study, all recurrences were reported to be within, or close to, the quadrant of the original tumor (10, 11). In the study by Liljegren*et al.* (9), a significantly greater rate of local recurrence was found in the arm receiving segmental mastectomy alone compared with the arm receiving segmental mastectomy and postoperative RT (18.4% vs. 2.3%). Again, 77% of the recurrences in the surgery-alone arm occurred within the initial tumor bed (9). A similar geographic pattern of local recurrence was recorded in the three other studies (6, 7). When the local recurrence data were classi-

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fied as "within" vs. "outside" the original tumor bed, the risk of recurrence outside the original tumor bed appeared to be equivalent (or inferior) to the risk of new primary cancers in the contralateral breast, which conventionally is not irradiated. The incidence of contralateral breast cancer for these studies was within the expected range of 0.5–1% annually. These data support the rationale for treating the original tumor bed as the area that could most benefit from the addition of adjuvant RT, omitting the remaining breast tissue in the ipsilateral and contralateral breast.

Limiting adjuvant RT to a volume inclusive of the tumor with sufficient margins among selected patients enabled the exploration of hypofractionated regimens (12–14). A number of protocols have since been developed with the intent of treating the original tumor bed with margins. This approach is based on the rationale that if much of the breast receives a dose below a clinically relevant threshold, it may be possible to treat a small volume with larger fraction sizes and maintain a low risk of late effects. Thus, through treatment of a smaller volume, it may be possible to avoid the classic dilemma encountered when a hypofractionated protocol is substituted for a standard treatment plan, which is the choice of either a reduced probability of tumor control or an increased risk of late complications (4, 5). Hypofractionated, partial breast irradiation (PBI) is actively being investigated by the use of several distinct techniques. Evidence is rapidly accumulating on the feasibility of performing PBI, as well as the need for careful patient selection and appropriate techniques to encompass the target volume adequately (15).

Although many PBI protocols are currently being used, relatively few data have been reported to justify the chosen schedules by predicting the biologic effects associated with the use of large-dose fractions delivered within a short period. Because it is possible to compare the anticipated biologic effects in terms of tumor control and normal tissue reactions by estimating a "biologic dose" through appropriate computations of biologically effective dose (BED) values, we report such calculations to compare the different PBI regimens with three commonly used protocols for whole breast RT.

METHODS AND MATERIALS

Breast RT protocols used in analysis

Standard fractionation studies. The fractionation regimen used for the RT component of breast conservation treatment has varied. The NSABP trials of breast preservation (16, 17), as well as the standard arm of the recent randomized Canadian trial studying whole breast hypofractionation (18), used 50 Gy in 25 fractions within 5 weeks ($Standard_{50}$). An alternative standard regimen is 46 Gy to the whole breast followed by an electron boost of 14 Gy to the tumor bed ($Standard_{60}$), a commonly used approach in the United States (19, 20).

In addition, the European Organization for Research and Treatment of Cancer has assessed the role of a boost to the tumor excision site (21–23). In this trial, the entire breast was irradiated with 50 Gy in 25 fractions followed by either no additional treatment or 16 Gy in 8 fractions (electron therapy or implantation) to a total dose of 66 Gy ($Standard_{66}$). At 5 years of follow-up, the use of the boost significantly reduced the local failure rate to 4.3% for patients randomized to receive the boost compared with 7.3% for those given whole breast treatment. These results suggest that irradiating the tumor bed with 66 Gy further reduces the local recurrence rate in breast conserving therapy. The main benefit was derived by patients <40 years, who demonstrated a 46% reduction in the rate of local recurrence at 5 years with the RT boost.

PBI studies. A variety of PBI protocols have been developed with the intent of treating the original tumor bed with margins; these are summarized in Tables 1, 2, and 3. PBI is based on the rationale that if much of the breast receives a very limited dose, it may be possible to treat with larger fraction sizes and maintain a low risk of late effects. A variety of treatment approaches have been used, including interstitial brachytherapy, MammoSite balloon brachytherapy, and external beam RT (EBRT) using three-dimensional conformal RT, intensity-modulated RT, or intraoperative electron beam RT (IORT). The design, treatment, and results of a series of brachytherapy PBI trials using both high-dose-rate and low-dose-rate brachytherapy included in the BED analysis are described in Table 1. With the exclusion of the Guy's Hospital study, which accepted patients with large tumors and positive margins, these series showed good local control rates of 0–16%, even if often reported with <5 years of follow-up. The European Institute of Oncology at the University of Milan, Italy has investigated IORT. They delivered electron beams of 3, 5, 7, or 9 MeV. Patients either received an IORT dose of 10–15 Gy after initial quadrantectomy with 1–2-cm clear margins, as an anticipated boost to EBRT, or an IORT dose of 17–21 Gy to the cavity as the only treatment (24).

An EBRT approach to PBI was first used at Christie Hospital. They compared EBRT PBI with whole breast RT for patients with tumors <4 cm in size. This study demonstrated a greater incidence of recurrence among infiltrating lobular histologic type tumors, 34% for PBI vs. 8% for whole breast RT (25), possibly reflecting the different natural biologic course between the two histologic types. Two different approaches of EBRT PBI have been reported from William Beaumont Hospital and New York University. The EBRT series are summarized in Table 2. Formenti *et al.* (26) pilot tested a Phase I feasibility study of hypofractionated conformal EBRT to the tumor bed (30 Gy in five fractions within 10 days) in a small series of selected postmenopausal women with T1 breast cancer, using immobilization in the prone position on a dedicated breast board (27). A Phase I-II study is currently ongoing at New York University. All patients completed treatment with only mild acute toxicity (28). Baglan *et al.* (29) also piloted an accelerated PBI protocol in patients with early-stage breast cancer. Three-dimensional conformal RT was used to treat

Table 1. Accelerated partial breast irradiation brachytherapy (HDR and LDR) and IORT studies

Series	Patients (*n*)	Age (y)	Tumor size (cm)	N stage	EIC	Margin status	Dose fractionation	Median follow-up (mo)	CTV margin (cm)	5-y Ipsilateral recurrence rate (%)
Guy's Hospital Trial (14, 71)	27	<70	<4	N0	Positive	Positive	HDR 55 Gy/5 d	72	2	37
Ochsner Clinic (72)	50	All	Tis and <4	N1	Positive	Negative	LDR 45 Gy/4 d	75	2–3	2
William Beaumont Hospital (13, 15, 73)	199	>40	<3	N0	Negative	Negative	HDR 4 Gy × 8 LDR 50 Gy/4 d	65	1–2	1
London Regional Cancer Centre, Canada (74, 75)	39	All	<5	N0	Positive	Positive	HDR 4 Gy × 8, 3.4 Gy × 10 HDR 3.72 Gy in 10 Fx b.i.d.	91	0	16.2
RTOG 95-17 (12)	100	All	<3	N1	Excluded	Negative	HDR 3.4 Gy × 10 b.i.d.	32	2	—
Virginia Commonwealth University (76)	44	All	<4	N1	Excluded	Negative	LDR 45 Gy/4 d LDR 45 Gy/4 d	42	1–2	0
Mammosite Multicenter Trial (77, 78)	43	>45	<2	N0	Excluded	Negative	HDR 3.4 Gy × 10 b.i.d. HDR 3.4 Gy × 10 b.i.d.	21	>1	—
National Institute of Oncology, Hungary (79)	Phase I-II, 45 Phase III, 63	All	<2	N0	Excluded	Negative	Ph I-II, HDR 4.33 Gy × 7, 5.2 Gy × 7; Phase III, HDR 5.2 Gy × 7	Phase I-II, 57 Phase III, 30	1–2	Phase I-II, 4.4 Phase III, 0
European Institute of Oncology (24)	101	All	<2.5	—	Excluded	Negative	IORT electron beam therapy 10–21 Gy	8	0	—

Abbreviations: HDR = high dose rate; LDR = low dose rate; IORT = intraoperative radiotherapy; EIC = extensive intraductal component; CTV = clinical target volume; b.i.d. = twice daily.

Table 2. Accelerated partial breast irradiation: EBRT studies

Series	Patients (*n*)	Age (y)	Tumor size (cm)	N stage	EIC	Dose fractionation	Median follow-up (mo)	Technique	Field arrangement	Tumor bed definition (CTV)	Margin (cm)	Ipsilateral breast recurrence rate (%)
Christie Hospital (25, 80)	353	<70	<4	N0	—	5 Gy × 8 in 10 d	96	Supine, 10-MeV electrons	Single electron beam	Tumor bed at surgery	0	6 (21/355)
NYU (26, 28)	47	Postmenopausal	<2	N0	Negative	6 Gy × 5 in 10 d	17	Prone, 6-MV photons	2 coplanar minitangents	Architectural distortion on CT	1.5–2	0
WBH (30, 31)	31	50	<3	N0	Negative	3.4 Gy × 10 in 5 d or 3.85 Gy × 10 in 5 d	10	Supine, 6-, 18-MV photons	3–5 noncoplanar beams	Architectural distortion and surgical clips on CT	1–1.5	—

Abbreviations: EBRT = external beam radiotherapy; NYU = New York University; WBH = William Beaumont Hospital; other abbreviations as in Table 1.

the lumpectomy cavity, plus a 1.5-cm margin. Their technique used an active breathing control method to account for breast movement related to respiratory excursion. More recently, Chen *et al.* (30) and Vicini *et al.* (31) published an update of their PBI experience using three-dimensional conformal RT. A dosimetric comparison of the William Beaumont and New York University EBRT PBI techniques is shown in Table 3.

Calculation of BEDs

The linear-quadratic model (32) was used to determine whether a partial breast RT protocol should result in a roughly equal probability of tumor control compared with a standard schedule, but without increasing the potential for normal tissue damage. The BED equation used for these calculations was

$$\mathrm{BED} = \mathrm{nd}\left(1 + \frac{\mathrm{d}}{\alpha/\beta}\right)$$

where n is the number of fractions, d is the dose per fraction, and α/β is a tissue- and effect-specific parameter associated with the linear-quadratic model (33–35).

A modification to this BED equation was also used to take into account the cellular proliferation that may take place during treatment:

$$\mathrm{BED} = \mathrm{nd}\left[1 + \frac{\mathrm{d}}{\alpha/\beta}\right] - \left[\frac{(\ln 2)\mathrm{T}}{\alpha(\mathrm{Tpot})}\right]$$

where T_{pot} is the potential doubling time and T is the treatment time during which cellular proliferation occurs after any initial lag period (33, 36–38).

Because an interfraction interval of at least 6 h was used for all the twice-daily high-dose-rate and EBRT treatments, it was likely that full repair of sublethal damage between fractions was permitted. It was, therefore, not necessary to include an incomplete repair factor in the equation used to calculate BEDs for these protocols.

The equation used to calculate the BEDs for the low-dose-rate treatments was

$$\mathrm{BED} = \mathrm{RT}\left\{1 + \left[\frac{2\mathrm{R}}{\mu(\alpha/\beta)}\right]\left[1 - \frac{1 - e^{-\mu T}}{\mu \mathrm{T}}\right]\right\}$$

where R is the dose rate, T is the length of the irradiation, and μ is the repair rate constant, which was equal to $ln2/t_{1/2}$, with $t_{1/2}$ the tissue repair half-time (39, 40).

RESULTS

BED values

Biologically effective dose calculations were performed for the three chosen standard whole breast EBRT protocols and 12 different hypofractionated PBI regimens delivered by EBRT,

Table 3. Dosimetric comparison of EBRT partial breast techniques

Series	PTV (cm^3)	PTV/TBV* (%)	Ipsilateral breast coverage 100%	75%	50%	25%	Lung dose† (%)	Cardiac dose‡ (%)
NYU (26)								
Median	192	22	27	40	46	53	0	0
Range	57–118	10–55	10–45	20–68	23–75	27–82	0	0
WBH (30, 31)								
Median	240	17	21	35	46	60	16	0‡
Range	82–482	11–22	14–39	26–53	34–60	39–92	0–37	0–7

Abbreviations as in Tables 1 and 2.
* Planning target volume/total breast volume.
† Percentage of lung volume that received 5 Gy.
‡ Percentage of cardiac volume that received 5 Gy (NYU) or 10 Gy (WBH).

high-dose-rate, and low-dose-rate techniques. The BEDs computed are listed in Tables 4 and 5 and shown in Fig. 1.

The selection of the α/β value used for these calculations was based on those reported in previous studies for the late effects of fibrosis and telangiectasia, in addition to the acute radiation reactions of erythema and desquamation; these values were 2, 4, 8, and 11 Gy, respectively (37, 41, 42). The tumor control BED values were determined using an α/β value of either 4 Gy, which has been suggested for breast carcinoma (43–46), or 10 Gy, which is the approximate value used for most tumors (46, 47). In addition, the BEDs were calculated for the low-dose-rate treatments assuming repair half times of 0.5, 1, 2, or 3 h. The repair kinetics for the tissues associated with acute and late responses, as well as breast carcinoma cells, are likely to fall within this range (48). As for the specific repair half-time appropriate for each effect, evidence has been obtained that sublethal damage repair

Table 4. EBRT and HDR brachytherapy BED values*

Institution (reference)	Protocol schedule	Fibrosis (α/β = 2 Gy)	Tumor control/ Telangiectasia (α/β = 4 Gy)	Erythema (α/β = 8 Gy)	Tumor control (α/β = 10 Gy)	Desquamation (α/β = 11 Gy)
$Standard_{50}$ (16–18)	2 Gy × 25	100	75	63	60	59
$Standard_{60}$ (19, 20)	2 Gy × 30	120	90	75	72	71
$Standard_{66}$ (21–23)	2 Gy × 33	132	99	83	79	78
London Regional Cancer Center (74, 75)	3.72 Gy × 10	106	72	54	51	50
Ochsner Clinic (72), William Beaumont Hospital (13, 15)	4 Gy × 8	96	64	48	45	44
National Institute of Oncology, Budapest, Hungary (79)	5.2 Gy × 7	131	84	60	55	54
	4.33 Gy × 7	96	63	47	43	42
William Beaumont Hospital (31)	3.85 Gy × 10	113	76	57	53	52
Christie Hospital (25, 80)	5 Gy × 8	140	90	65	60	58
New York University (26, 28)	6 Gy × 5	120	75	53	48	46
RTOG 95-17 (12), Mammosite Multicenter Trial (77), Virginia Commonwealth University (76), William Beaumont Hospital (15)	3.4 Gy × 10	92	63	48	46	45
European Institute of Oncology (24, 81)	21 Gy × 1†	241	131	76	65	61

Abbreviations: BED = biologically effective dose; $Standard_{50}$ = whole breast to 50 Gy in 25 fractions; $Standard_{60}$ = whole breast to 46 Gy in 23 fractions plus 14 Gy in 7 fractions to tumor bed (total 60 Gy); $Standard_{66}$ = whole breast to 50 Gy in 25 fractions plus 16 Gy in 8 fractions to tumor bed (total, 66 Gy); RTOG = Radiation Therapy Oncology Group; other abbreviations as in Tables 1 and 2.
* BED values given in Gray.
† The formula used to calculate BED may not yield an accurate value for a single fraction treatment.

Table 5. LDR brachytherapy BED values

Series	Repair half-time (h)	Fibrosis (α/β = 2 Gy)	Tumor control/ telangiectasia (α/β = 4 Gy)	Erythema (α/β = 8 Gy)	Tumor control (α/β = 10 Gy)	Desquamation (α/β = 11 Gy)
Ochsner Clinic (72) 45 Gy in 4 d						
	0.5	60	53	49	48	48
	1	76	60	53	51	51
	2	104	75	60	57	56
	3	133	89	67	63	61
Guy's Hospital (14, 71) 55 Gy in 5 d						
	0.5	73	64	60	59	58
	1	91	73	64	62	62
	2	127	91	73	69	68
	3	161	108	81	76	74
WBH (13) 50 Gy in 4 d						
	0.5	69	59	55	54	53
	1	87	68	59	57	57
	2	123	86	68	65	63
	3	157	103	77	71	69

Abbreviations: BED = biologically effective dose; other abbreviations as in Table 2.

rates are often slower for late-responding normal tissues compared with either early-responding normal tissues or tumors (48, 49), although in some instances, this generalization may not be correct (50–52).

BED calculations taking into account tumor repopulation

It should be noted that all the PBI treatments were accelerated schedules, because the total dose was delivered in less time than with the standard whole breast protocols. Therefore, relatively little cellular proliferation is likely to occur during the course of these treatments compared with the standard protocols, in which it is probable that more extensive repopulation will take place, thereby both decreasing the chances for tumor control and reducing the severity of acute radiation responses. The lack of tumor repopulation represents a potential advantage to the use of an accelerated partial breast protocol compared with a standard treatment, and the BEDs were also calculated assuming cell repopulation during treatment. To accomplish this, it was necessary to select values for α, the initial slope of the cell survival curve, as well as for T_{pot} and T. For the purpose of these calculations, values of 0.3 for α (43, 44), 13 days for T_{pot} (53, 54), and a time lag of 14 days were used. However, it must be stressed that the actual values for any given patient may differ significantly. This correction for cell proliferation causes the tumor and acute response standard treatment BED values to decrease by approximately 3–5 Gy. No change would be expected in the fibrosis or telangiectasia BEDs, because compensatory proliferation would not be expected to begin until after treatment was complete. In addition, no correction was made to any of the PBI schedules, because all these treatments are accomplished within a period that is shorter than the lag period even in the tumor and acutely responding normal tissues. Taking possible tumor growth during treatment into consideration results in a closer alignment of BED values between the PBI and standard schedules. If cell proliferation is considered, this also diminishes the BEDs of the early responses for the standard schedules compared with the accelerated PBI schedules. However, it would still be anticipated, based on the computed BEDs and only a portion of the breast being irradiated, that the severity of the early responses would remain lower for the PBI treatments compared with the standard protocols.

DISCUSSION

The current work compared BED values at the tumor bed/boost area for the PBI regimens vs. those from standard whole breast RT protocols. The tumor control BED values computed for the PBI protocols were uniformly lower than the BEDs for any of the standard schedules when these calculations were performed using an α/β of 10 Gy, considered typical of most tumors (46, 47). In contrast to this generalization, evidence exists from *in vitro* studies that breast carcinoma cell lines display an α/β value of about 4 Gy (43–46). Use of this α/β, with correction for cellular proliferation, yielded BED values for the PBI treatments that were generally comparable to the BED obtained for $Standard_{50}$. However, when compared with either $Standard_{60}$, a fractionation regimen commonly used in the United States, or $Standard_{66}$, the BED values were nearly all lower for the PBI treatments. This is of significance because of available evidence

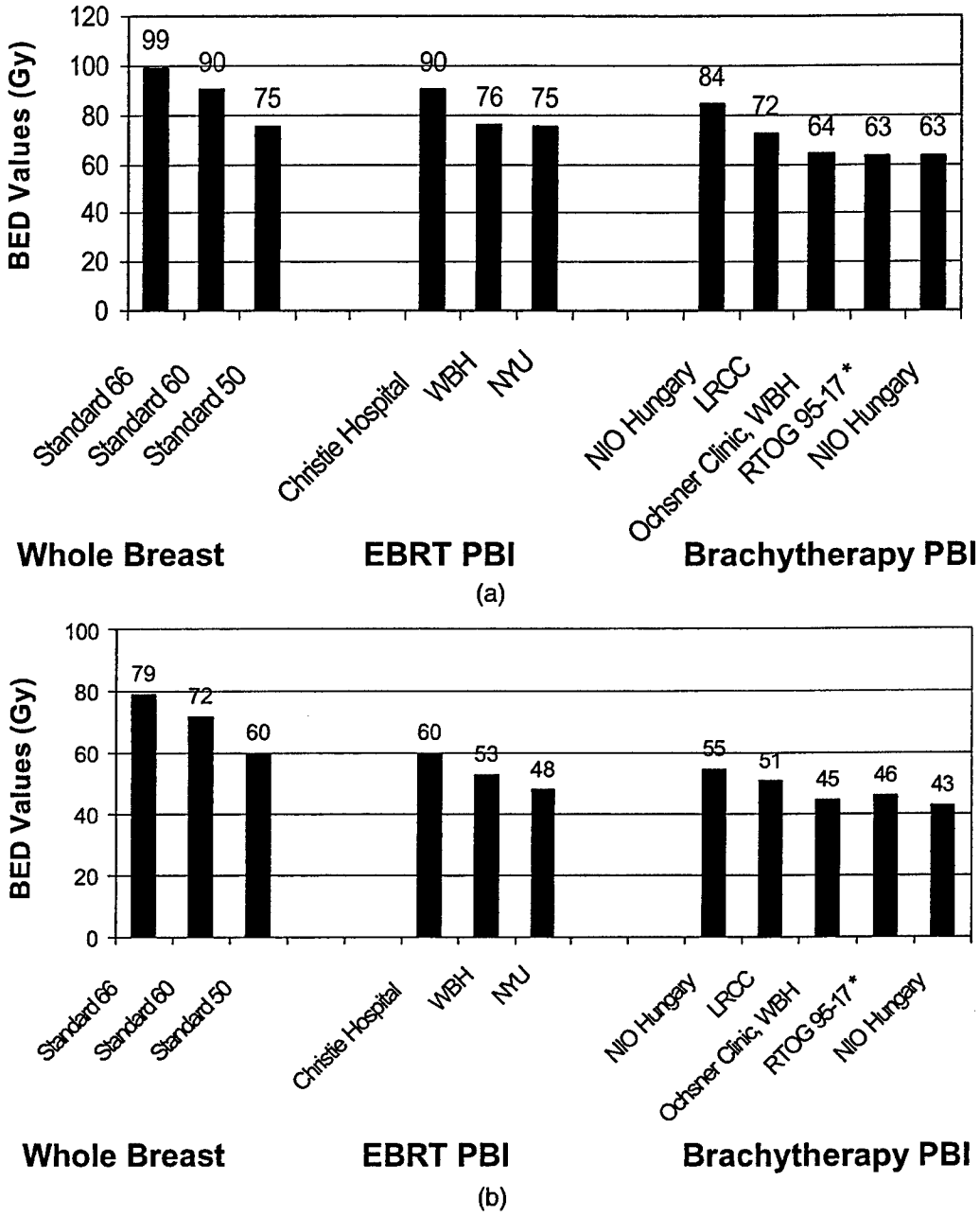
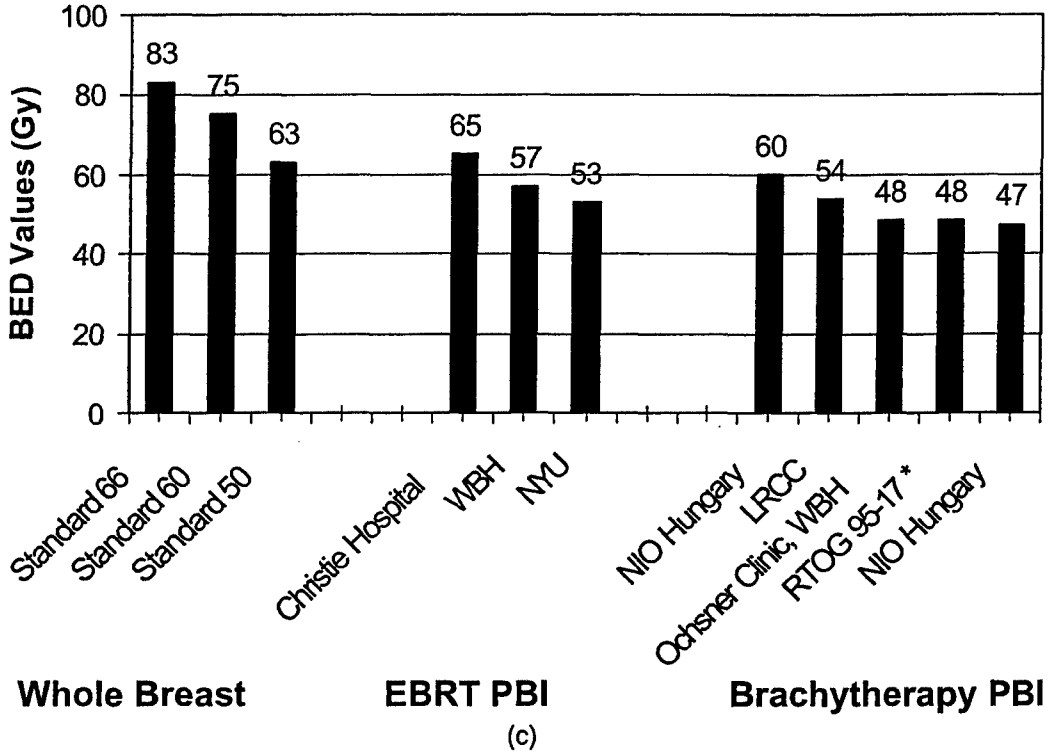


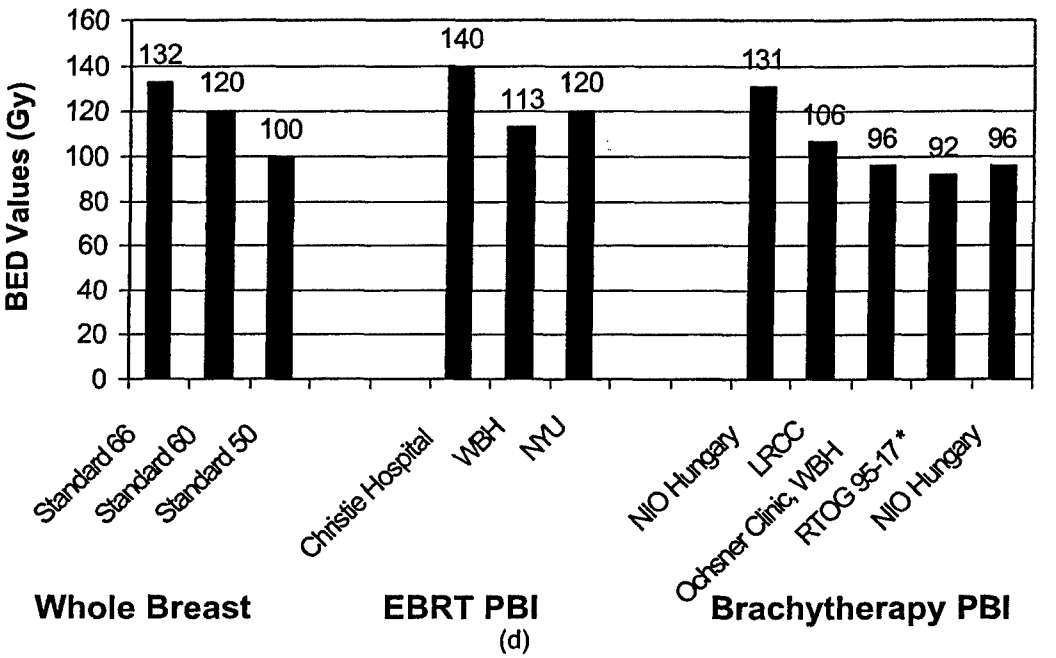
Fig. 1. Histograms demonstrating biologically effective dose (BED) values for partial breast irradiation (PBI), external beam radiotherapy (EBRT), and brachytherapy protocols compared with standard whole breast protocols for tumor control, acute effects, and late effects. BED values for PBI protocols for tumor control with (a) α/β of 4 Gy and (b) α/β of 10. BEDs for PBI protocols for (c) acute effects (erythema, α/β of 8 Gy) and (d) late effects (fibrosis, α/β = 2 Gy). Same fractionation used in Mammosite Multicenter Trial, Virginia Commonwealth University and William Beaumont Hospital.

showing a dose–response effect at the boost site, as demonstrated by the finding that the Standard_{66} treatment resulted in a decreased incidence of tumor recurrence compared with the Standard_{50} (22).

It is important to note, however, that a basic assumption often made in the use of BED values to predict a particular level of tumor control or normal tissue damage is that the probability of tumor control or the development of a normal tissue radiation effect is linearly proportional to the BED. This may be correct for certain doses, but it is not true across an entire dose range (55). That is, the tumor control probability may already be sufficiently high, so that it is in a "plateau" region where relatively little benefit would be expected with increasing dose. Similarly, the normal tissue effect curve may be at a level below a threshold for a particular radiation response so that increasing the BED would still have no impact, as long as the threshold were not exceeded.



(c)



(d)

Fig. 1 (*Continued*).

However, the evidence from the European Organization for Research and Treatment of Cancer boost trial (22) suggests that the doses tested by the PBI trials were less than this theoretical plateau.

Also, the use of relatively large doses per fraction in PBI protocols presents specific radiobiologic concerns because of a possible reduction in reoxygenation and reassortment (56). This is particularly relevant to the case of IORT in which only one fraction is delivered at a high dose rate. It is well known that because solid tumors often outgrow their neovasculature, viable cells may be present that exist in a relatively low oxygen concentration (57, 58). This radioresistance of hypoxic tumor cells is usually overcome through the delivery of a treatment dose in a series of fractions during a period of weeks, enabling hypoxic cells to reoxygenate and regain a normal level of radiosensitivity (59, 60).

Another concern regarding the use of a single fraction is the inability of cells to reassort through the cell cycle. Cells in more radioresistant phases of the cell cycle, such as the S phase, tend to exhibit a greater level of survival compared with cells in more radiosensitive phases, such as G_2 or mitosis (61).

In a standard fractionation protocol, the surviving cells continue progression in the cell cycle so that at the next RT session, the cells may be located in a more radiosensitive phase and, therefore, be killed. Normally, this sensitization associated with fractionation is beneficial, because tumor cells are generally more actively progressing through the cell cycle compared with cells that comprise late-responding tissues.

A more generalized problem affecting all PBI techniques is that a significant volume of normal breast tissue receives a relatively low, but potentially carcinogenic, radiation dose, thereby possibly increasing the probability of secondary malignancies (62). Although the available data suggest that the cancer risk remains elevated across a large dose range (63), it may also be possible that the relatively high doses associated with whole breast RT carry a low risk of inducing a new tumor, because a dose of 40–50 Gy may primarily cause cellular lethality rather than neoplastic transformation. In contrast, for all of the PBI techniques, a substantial portion of the breast receives a comparatively low noncytocidal dose. Potentially, PBI should be limited to an older population of women who would have a lower risk of developing secondary malignancies.

Because the therapeutic ratio for postsegmental mastectomy is a balance between local control and an acceptable risk of late effects, even after successful modeling of tumor/normal tissue effects, the central issue of optimal patient selection remains unsolved. Ideally, only those patients who carry a risk of recurrence/new primary in the breast tissue outside the target of PBI that is expected to be roughly equal to that of the contralateral, conventionally nonirradiated breast, should be offered this alternative treatment approach. The available data suggest that these women are likely to be postmenopausal carriers of hormonally sensitive, mammographically detected breast cancers. Noticeably, these women are also likely to undergo systemic antihormonal treatment to reduce their bilateral breast cancer risk. Because of the high cure rate these women are likely to enjoy after standard treatment, it is very important to study PBI rigorously, especially in regard to its risk of long-term sequelae and second malignancies (17).

For most of the published brachytherapy protocols with long follow-up, the total breast dose–volume histogram data have not been reported. Therefore, in the absence of this information, it is not possible to compute BED values that take into account partial breast volumes (64, 65). It is hoped that future publications will contain this information so that it will be possible to compute integrated BEDs (66) for regions outside of the target volume representing normal breast tissue.

In addition, the follow-up for both the brachytherapy and EBRT techniques is too short for adequate assessment of long-term toxicity and fibrosis. As demonstrated in a series from the M. D. Anderson Cancer Center, the length of time to the expression of 90% of the ultimate frequency of fibrosis and telangiectasia was 4.7 years (95% confidence interval, 4.0–4.8) (4). For all the PBI regimens, careful follow-up and analysis of patients for late effects will help ascertain whether increased late effects will be seen in patients treated with hypofractionated protocols.

As a final note, increasing interest has focused on the role that genetic factors may play in radiosensitivity. Evidence is mounting that genetic alterations present in certain genes associated with radiation responses, such as *ATM* (67, 68), *TGF-β* (69), *SOD, XRCC1,* and *XRCC3* (70), may play an important role rendering some patients radiosensitive. If true, it is possible that the patients with these genetic alterations may represent essentially a radiosensitive subpopulation, possibly comprising 5–10% of women who develop breast cancer. These women may be the most likely candidates to develop radiation responses such as fibrosis, telangiectasia, or chronic skin changes after RT completion. If it were feasible to identify these patients prospectively before the start of RT, they could be spared the risk of late radiation effects that may be associated with PBI treatment. Although this is not currently practical, with the advances being made in DNA sequencing, the time may not be far off when many breast cancer patients will arrive at their initial consultation with a radiation oncologist, armed with the DNA sequence of their entire genome. With this information, and the knowledge as to the important genetic alterations associated with radiosensitivity, the radiation oncologist may then be able to tailor the RT so that it is appropriate for each patient and thus to increase the probability of tumor control and diminish the risk of normal tissue late effects.

CONCLUSION

The PBI protocols that have been developed, and are currently being tested in clinical trials, yield BED values that are generally comparable to the Standard_{50} schedule, corrected for tumor repopulation during treatment. However, the PBI BEDs are consistently lower than the BEDs for either the Standard_{60} or Standard_{66}. Therefore, it may be anticipated that the tumor control rates, at least in the field receiving the full treatment dose, may be lower for the PBI regimens compared with standard whole breast RT using an additional boost dose to the tumor bed. Finding the balance between adequate imaging and irradiation of the target and limiting the breast volume receiving the full treatment dose to avoid an increased probability of late radiation sequelae, together with correct selection of patients at low risk of recurrences outside the target volume, underlie the successful outcome of PBI trials. An additional concern associated with the use of PBI is the unknown risk of second malignancies in the remaining breast tissue, outside the PBI volume. For all these reasons, and because equivalence to standard protocols for both efficacy and morbidity has yet to be proved, PBI protocols remain investigational.

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Seminars in
RADIATION
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External-Beam Partial-Breast Irradiation

Silvia C. Formenti, MD

Although most studies treating patients with partial-breast irradiation have used brachytherapy, giving such treatment with external-beam techniques has many potential advantages. However, there is only limited published experience using this approach. These include a randomized trial of partial-breast and whole-breast irradiation performed at the Christie Hospital in Manchester, England, and pilot studies (using much more rigorous selection criteria and sophisticated treatment planning) from groups at the University of Southern California, New York University (using prone positioning of patients), and the William Beaumont Hospital (using the supine position). A multi-institutional pilot trial based on the latter technique has been completed, which was designed to test the feasibility of using this approach in the cooperative oncology group setting. The unprecedented rapidity with which the study completed its target accrual indicates the degree of interest in this approach. This review focuses on the rationale and the reported studies of external-beam partial-breast radiation and identifies some specific issues and remaining problems associated with this approach.

Although most studies treating patients with partial-breast irradiation (PBI) have used brachytherapy, in theory an external-beam approach to PBI (EB-PBI) has many potential advantages. First, it easily allows treatment to be given after lumpectomy when complete pathological information about the original tumor and the status of the resection margins are available, without subjecting the patient to a second invasive surgical procedure or anesthesia. Second, it is likely that EB-PBI will be easier for radiation oncologists and cooperative oncology groups to adopt than brachytherapy approaches because the technical demands and quality assurance issues are much simpler. Third, treatment results with EB-PBI may be more uniform between radiation oncologists because the outcome depends less on the experience and operative skills of the person performing the procedure than does brachytherapy (especially using interstitial implantation). Fourth, it seems less likely that technical issues arising during EB-PBI will require the procedure to be aborted, as is not infrequently the case when brachytherapy techniques are used. Fifth, EB-PBI is intrinsically likely to generate better dose homogeneity and thus possibly may result in a better cosmetic outcome when compared with brachytherapy. Finally, EB-PBI may be considerably cheaper than brachytherapy techniques, especially if an extra surgical procedure and (for low-dose rate brachytherapy) hospitalization are needed.[1,2]

Despite these theoretical advantages, there has been very little study of EB-PBI. This may be because of the difficulty of adequately locating the excision cavity and planning multifield photon treatment plans in the era before computed tomography (CT)-based simulation. At present, there are only a few published experiences using EB-PBI. These include a randomized trial comparing partial-breast and whole-breast irradiation performed in England[3,4,5] and pilot studies (using much more rigorous selection criteria and sophisticated treatment planning) from groups at the University of Southern California and New York University[6-8] (using prone positioning of patients) and the William Beaumont Hospital (using the supine position).[9,10] A multi-institutional pilot trial based on the latter technique was recently conducted by the Radiation Therapy Oncology Group (RTOG 0319) under the direction of Dr Frank Vicini to test the feasibility of using this approach in the cooperative oncology group setting, and the study rapidly completed its target accrual.

This review therefore focuses on the techniques and reported outcome of reported studies of EB-PBI. I will also

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identify some specific issues and problems associated with this approach.

A Phase III Trial of EB-PBI

Only 1 prospective randomized trial has been performed to compare the efficacy of EB-PBI to whole-breast radiotherapy. This trial was conducted at the Christie Hospital, Manchester, United Kingdom.[3-5] Seven hundred eight patients with tumors 4 cm or smaller of infiltrating ductal or lobular histology were randomized after segmental mastectomy to undergo radiation to a small breast field, including the tumor bed (the limited field [LF] arm) or to the whole breast and regional nodes (the wide field [WF] arm). The 2 arms differed in field size, treatment modality, and dose fractionation. For the LF arm, the dose given was 40 to 42.5 Gy in 8 fractions delivered over 10 days, using 8 to 14 MeV electrons (prescribed to the 100% isodose line) with an average field size of 8 × 6 cm. For the WF arm, the dose was 40 Gy in 15 fractions, over 21 days, delivered by opposed tangential fields to the breast and a separate anterior supraclavicular/axillary nodal field using 4-MV photons.

With a median follow-up of 65 months, the 8-year actuarial overall survival rates were comparable between the arms (73% and 71% for the LF and WF groups, respectively). The actuarial breast recurrence rates (scoring only first failure sites) were 20% for patients in the LF arm and 11% for patients in the WF arm ($P = 0.0008$). However, when the data were analyzed according to histological type, the risks of local failure in patients with infiltrating ductal carcinoma were 15% in the LF and 11% in the WF arm, whereas, for patients with infiltrating lobular carcinoma, the respective recurrence rates was 34% and 8%. A high recurrence rate was found in both arms for patients with extensive ductal carcinoma in situ (21% and 14%, respectively). Importantly, the failure rate outside the quadrant of the original tumor for patients with IDC in the LF arm was only 5.5%. Salvage surgery was possible in 86% and 90% of patients in each arm, respectively. Cosmetic results were worse in the LF arm than the WF arm, with much more fibrosis and telangiectasias in the former group. The authors concluded that, although the recurrence rate in the breast after lumpectomy and wide field irradiation was comparable with others reported in the literature of the time, in selected subsets of patients limited field irradiation resulted in a higher breast recurrence rate.[4]

There were many differences in the way patients in this trial were managed and how patients are treated today. Axillary dissection was not performed, and systemic therapy was not used. Most patients did not have pre- or postoperative mammographic evaluation, and specimen margins were not evaluated microscopically. Therefore, although the local failure rate was considerably higher in the LF arm than the WF arm for the population as a whole, the much smaller difference between the arms for patients with infiltrating ductal carcinomas actually is quite encouraging that the approach of EB-PBI is worth pursuing. The high rate of telangiectasias in the LF arm is not surprising, considering the high skin dose delivered by pure electron beams, but the increased risk of fibrosis may also be a problem facing EB-PBI approaches using photons. This issue will be discussed at some length later.

Prone EB-PBI

Rationale for Prone Patient Positioning

One common challenge that must be addressed by any technique of breast radiotherapy is the anatomic/geometric constraints required to treat the breast tissue volume, a target that is generally shaped as a concave, irregular dome. Although several techniques have been studied, treatment of the entire breast using opposed tangent fields in the supine position tends to include some part of the lung and, for left-sided tumors, the heart. Moreover, respiratory and systolic motion often increase the amount of normal tissue unnecessarily treated.

Positioning patients prone considerably reduces the breast tissue motion because of both cardiac systole and respiration,[11] limiting the excursion of the chest wall to less than 5 mm.[12] In addition, prone positioning allows for exclusion of lung and heart tissue from the treatment fields.[13] This is particularly important in view of the growing evidence that treatment of these organs may cause late morbidity.[14-17] Most importantly, if patients are placed on a special tabletop that has a hole in it (Fig. 1) that allows the breast tissue to fall away from the chest wall, the excision cavity can be treated by fields that do not include any portions of the heart or lungs. Figure 2 shows how both the shape and the position of the excision cavity vary when the same patient is imaged either in the supine (Fig. 2A) or prone position (Fig. 2B). When prone, the cavity tends to be dislocated away from the chest wall by gravity.

Initial Studies of Our Group Using the Prone Position

Based on these considerations, we initiated a research program at the University of Southern California, Los Angeles, to study EB-PBI given in the prone position. We started by exploring the physical and dosimetric aspects of multiple noncoplanar fields directed toward the tumor bed in the prone patient.[12] The first dedicated table for prone partial-breast treatment was designed. Dosimetry was analyzed for 2 "radiosurgical" approaches, one using 7 fixed horizontal beams and the second using six 45° arcs and a 90° sagittal arc; both used a 4-MV x-ray beam with a 32-mm diameter collimator. Both field arrangements resulted in adequate tumor coverage; the minimum target dose was 83% of the dose maximum in the fixed-beam arrangement and 86% in the multiarc setup.

Originally, we had envisaged using this approach in a radiosurgery-like fashion, with the long-term aim of substituting breast radiosurgery for surgical excision for patients with breast cancers measuring 5 mm or smaller. However, although giving such radiosurgery-like treatment was feasible technically, planned excisions performed 8 to 10 weeks later in the first 3 patients so treated with 15, 18, and 20 Gy

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Figure 1 Example of a patient undergoing CT simulation in prone position, on a dedicated treatment table designed for partial-breast radiation.

showed that residual viable tumor was consistently within the treated target volume. This was despite the careful selection of the study patients, who each had a tiny mammographically detected tumor, marked by a tantalum clip placed at the time of core biopsy. This small but significant experience redirected the research goal to the exploration of a hypofractionated approach, directed to treat the postoperative tumor cavity with added margins.

Selection of a Dose-Fractionation Scheme for Our Subsequent Pilot Trial of Postoperative Hypofractionated PBI

The accessibility of the target in patients treated in the prone position, unencumbered by constraints of treating surrounding normal lung or heart tissue, together with the relatively small volume associated with PBI created the ideal conditions to safely explore an accelerated, hypofractionated regimen.

At the time, the only prospective randomized study on this issue was that of Baillet and colleagues[18] at the Necker Hospital in Paris. They reported equivalent local control but inferior cosmetic results at 4 years in elderly patients receiving a hypofractionated regimen of 23 Gy delivered in 4 fractions over 3 weeks to the entire breast, compared with a regimen of 45 Gy in 25 fractions given in 5 weeks. Therefore, it became necessary to derive a rational dose-fractionation regimen of accelerated radiation therapy from published preclinical and clinical data.

By applying the linear-quadratic cell survival model with an alpha-beta value for breast carcinoma of 4,[19-21] a dose of 30 Gy given in 5 fractions of 6 Gy per fraction over 10 days was found radiobiologically equivalent in tumor control to a dose of 50 Gy given in 25 fractions of 2 Gy over 5 weeks, which is the dose commonly used in studies of the National Surgical Adjuvant Breast And Bowel Project.[22] At the same time, this hypofractionated scheme resulted in the same biologic equivalent dose (BED) for late breast tissue complications[23] (including desquamation, fibrosis, erythema, and telangiectasia) as that of 60 Gy in 30 fractions, a regimen used at many institutions to treat the tumor bed (46-50 Gy to the whole breast plus a boost of 10-14 Gy), which has been reported to have excellent cosmetic results.[24] Table 1 compares the BED values for these 3 different fractionation regimens and for the fractionation regimen used in supine EB-PBI for different endpoints.

Rationale for Patient Selection Criteria for Our Postoperative Hypofractionated Pilot Trial

The impetus for investigating prone EB-PBI was the epidemiological evidence of a rapidly emerging new breast cancer population in the United States because of the widespread use of mammographic screening: postmenopausal women with small, estrogen receptor–positive tumors, who commonly have negative nodes and 5- and 10-year survival rates of 95% and 85%, respectively.[25,26] Because of the limited risk of breast cancer death in this subset of patients, the likelihood that potentially suboptimal radiation therapy would affect survival seemed very small, making it acceptable to conduct trials exploring PBI in this group. Moreover, there is evidence that postoperative radiation therapy has often been omitted for elderly women, especially those with significant comorbid conditions because of concern that they will not be able to complete (for medical or logistical reasons) 6 weeks of daily treatment.[27-29] It appeared that a more cost-effective, user-

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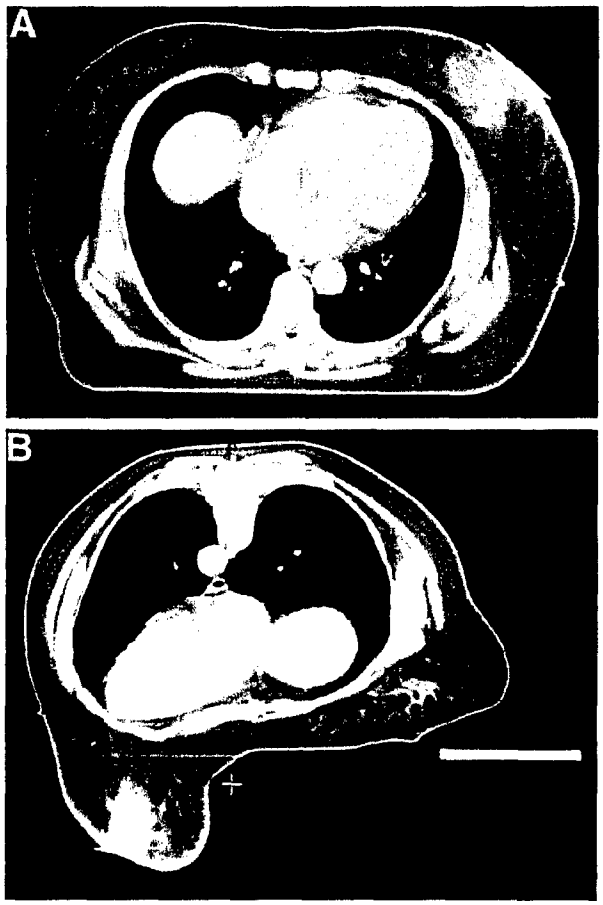

Figure 2 One month after breast surgery, the same patient as in Figure 1 was scanned both in the supine (Fig. 2A) and prone (Fig. 2B) positions. Radio-opaque markers were placed while supine to define the lateral extent of the breast and to identify the lumpectomy scar. A supine and a prone scan at the level of the lateral marker are shown to exemplify how the shape and site of the postsegmental excision seroma varies based on patient's position. When prone, the cavity elongates and is more distant from the chest wall.

friendly regimen could best satisfy the needs of this specific population, ideally without compromising local recurrence control and breast cancer survival. Finally, a radiotherapy technique that completely avoids including any of the lung or heart is particularly appealing in a patient population in which late cardiovascular effects might be added to preexisting illness.

Results of Our Pilot Phase I Trial (University of Southern California)

From January 1997 to June 1998, we conducted a pilot dose-escalation study of hypofractionated conformal EB-PBI external-beam radiotherapy to the tumor bed in selected postmenopausal women with T1 breast cancers consecutively seen at the University of Southern California.[6] All patients were required to be postmenopausal, with nonpalpable, mammographically detected tumors measuring less than 1 cm in diameter, which were excised with negative margins, with pathologically negative axillary lymph nodes. The study randomly assigned cohorts of 3 patients each to 3 dose levels (5 fractions of 5, 5.5, or 6 Gy each, respectively, delivered over 10 days). Treatment was found to be feasible in 9 of 10 consecutive patients; the only excluded patient had a tumor cavity that was extremely lateral (in the tail of Spence), and it was determined that she was best treated supine. With a minimum follow-up of 3 years, there were no recurrences and all patients had "good or excellent" cosmetic results.

Preliminary Results of Our Subsequent Phase I/II Study (New York University)

Because of these encouraging results, we designed a phase I/II study that opened at New York University in 2000 and is ongoing. Results on the first 47 patients entered (of the total accrual goal of 99 patients) have been recently reported.[7,8] Five fractions of 6 Gy each are delivered over 10 days, for a total dose of 30 Gy. After taking a planning CT in the prone position, the postsurgical cavity is defined as the clinical target volume (CTV), and a 1.5-cm margin is added to generate the planning target volume (PTV). An example is given in Figure 3. In this case, opposed tangential fields with 15° wedges were used. The corresponding dose-volume histogram results show that less than 45% of the ipsilateral breast volume received more than 50% of the prescribed dose. F3

For the 47 patients currently on study, the mean volume of the ipsilateral breast receiving 100% of the prescribed dose was 26% (range, 10%-45%), whereas the mean volume of the breast contained within the 50% isodose surface was 47% (range, 23%-75%). The lung and heart were consistently spared. Acute toxicity was modest, limited mainly to grade 1

Table 1 Biologically Equivalent Doses of Different Fractionation Schemes

Endpoint	α/β	50 Gy/25 fx	30 Gy/5 fx	60 Gy/30 fx	34 Gy/10 fx
Erythema	8†	63 Gy_8	53 Gy_8	75 Gy_8	48 Gy_8
Desquamation	11†	59 Gy_{11}	6 Gy_{11}	71 Gy_{11}	45 Gy_{11}
Telangiectasia	4†	75 Gy_4	75 Gy_4	90 Gy_4	63 Gy_4
Fibrosis	2†	100 Gy_2	120 Gy_2	120 Gy_2	92 Gy_2
Tumor control*	4	75 Gy_4	75 Gy_4	90 Gy_4	63 Gy_4
Tumor control*	4	72 Gy_4	75 Gy_4	86 Gy_4	63 Gy_4

*Taking into account cell proliferation during the course of treatment.[19,38,21]
†Data from Archambeau et al.[23]

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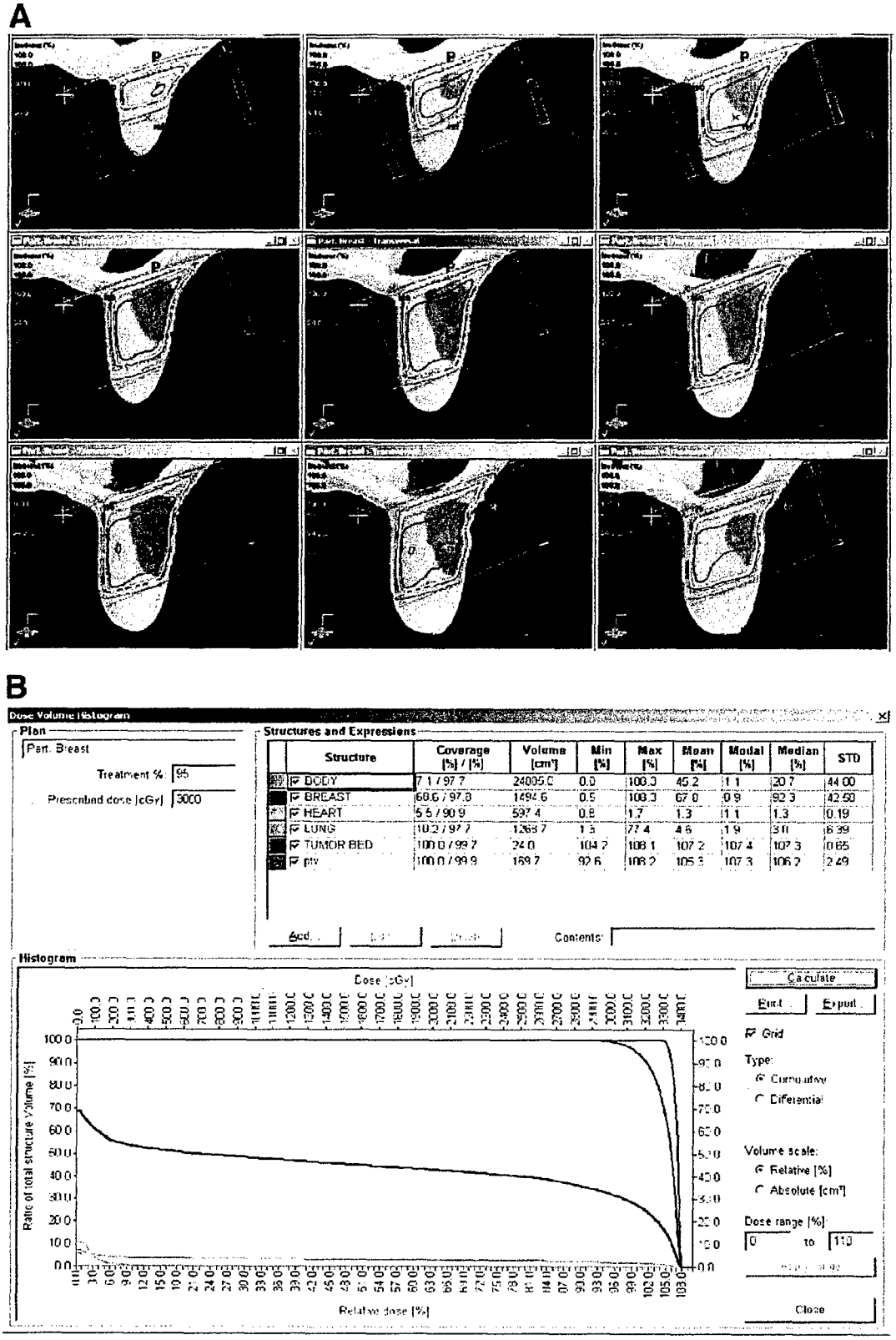

Figure 3 (A) A set of transverse CT slices (acquired every 0.37 cm, but here displayed every 0.75 cm) for a prone EB-PBI treatment are shown, with isodose distribution around the tumor bed (CTV, shown in red) and around the PTV (shown in magenta). Opposed tangential fields with 15° wedges were used to improve dose homogeneity. (B) Dose volume histograms of the treatment plan are shown.

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to 2 erythema. With a median follow-up of 18 months, only grade 1 late toxicity has occurred, and no patient has developed a local recurrence.

Studies of Supine EB-PBI

William Beaumont Hospital Experience

The group at William Beaumont Hospital, near Detroit, pilot-tested giving supine accelerated PBI in 9 patients, using active breathing control to compensate for breast movement related to respiratory excursion.[9] The dose-fractionation scheme initially chosen was nominally the same as in their brachytherapy PBI experience. The first five patients received 34 Gy in 10 fractions, given twice daily over 5 days, while the following four patients received 38.5 Gy in 10 fractions. The technique appeared to be feasible and well tolerated.

Based on this preliminary data, Vicini and colleagues[10] conducted a phase I-II study in 31 patients, using eligibility criteria similar to those applied in RTOG trial 95 to 17. Most patients (29/31) had surgical clips placed at the time of surgery to define the lumpectomy cavity. The CTV consisted of the lumpectomy cavity plus a 10- to 15-mm margin. The PTV consisted of the clinical target volume plus a 1-cm margin to account for breathing motion and daily variability of treatment setup. Active breathing control was not used in this study. In the first 6 patients, the prescribed dose was 34 Gy in 10 fractions given twice daily (with a minimum 6-hour interfraction interval) over 5 consecutive days, whereas for the subsequent 25 patients, the prescribed dose was increased to 38.5 Gy in 10 fractions. The study was designed to treat the clinical target volume with less than 10% inhomogeneity and to give a comparable or lower dose to the heart, lung, and contralateral breast than standard whole-breast tangents.

At the time of publication, the median follow-up time for this cohort was 10 months (range, 1-30 months). The only toxicity during treatment was grade 1 erythema. At the initial 4- to 8-week follow-up visit, 19 patients (61%) experienced grade 1 toxicity and 3 patients (10%) grade 2 skin toxicity. No grade 3 toxicities were observed. The remaining 9 patients (29%) had no observable radiation effects. Cosmetic results were rated as good or excellent in all evaluable patients at 6 months (n = 3), 12 months (n = 5), 18 months (n = 6), and in the 4 evaluable patients followed more than 2 years after treatment. The mean coverage of the clinical target volume by the 100% isodose line (IDL) was 98% (range, 54%-100%, median: 100%); its coverage by the 95% IDL was 100% (range, 99%-100%). The mean coverage of the planning target volume by the 95% IDL was 100% (range, 97%-100%). The mean percentage of the breast receiving 100% of the prescribed dose was 23% (range, 14%-39%), whereas the mean percentage of the breast receiving 50% of the prescribed dose was 47% (range, 34%-60%). The study supported feasibility of this approach and generated the background experience for RTOG 0319.

RTOG 0319: A Multicenter Phase I/II Trial to Evaluate Three-Dimensional Conformal Radiation Therapy Confined to the Region of the Lumpectomy Cavity for Stage I and II Breast Cancer

This study assesses the technical feasibility and acute toxicity of irradiating the region of the tumor bed (identified by surgical clips placed at the time of lumpectomy) with 3-dimensional conformal radiation therapy. Eligible to the trial were newly diagnosed breast cancer patients with stage I to II disease and negative margins of excision (at least 2 mm) after lumpectomy. Patients with up to 3 positive nodes were eligible. Patients were excluded if they had tumors larger than 3 cm, lobular histology, or if an extensive intraductal component was present. A dose per fraction of 3.85 Gy was delivered twice daily, with each treatment separated by a minimum of 6 hours, for a total dose of 38.5 Gy given in 10 consecutive fractions (delivered from Monday to Friday). The planned accrual of 46 patients was rapidly achieved. Results are not yet available.

Other Studies

A few other groups have begun studies of EB-PBI in the supine position. These include investigators at Evanston Northwestern Health care in Evanston, IL (giving a dose of 43.2 Gy in 16 once-daily fractions using intensity-modulated radiation therapy),[30] and at the institutions of the Dana-Farber/Harvard Cancer Center in Boston, MA (giving 32 Gy in 8 fractions, delivered twice daily, using conformal photon or mixed photon-electron plans).[31] So far, only very early results are available that show such treatment is feasible with minimal acute toxicity.

Potential Pitfalls of External-Beam Partial-Breast Irradiation

Preliminary experience with EB-PBI has identified common problems that investigators are likely to encounter with this approach. One is the correct identification of the excision cavity. The ability of the radiation oncologist to correctly target treatment depends on the type of surgical technique used as well as the time interval between excision and treatment planning. Placing surgical clips at the time of segmental mastectomy to define the cavity boundaries has the advantage of permanently marking the site of excision, but migration of clips after placement has been reported, making reliance on the technique questionable.[32] Usually, the postoperative cavity can easily be identified within a few weeks after lumpectomy because of the seroma that rapidly forms, which has fluid-like density and can be easily identified at CT planning. However, if there is too long of a delay between surgery and simulation, the cavity may be very difficult to see. However, if treatment planning is done too soon, it is possible that the lumpectomy cavity and breast will change in size and shape between the time of treatment planning and initial

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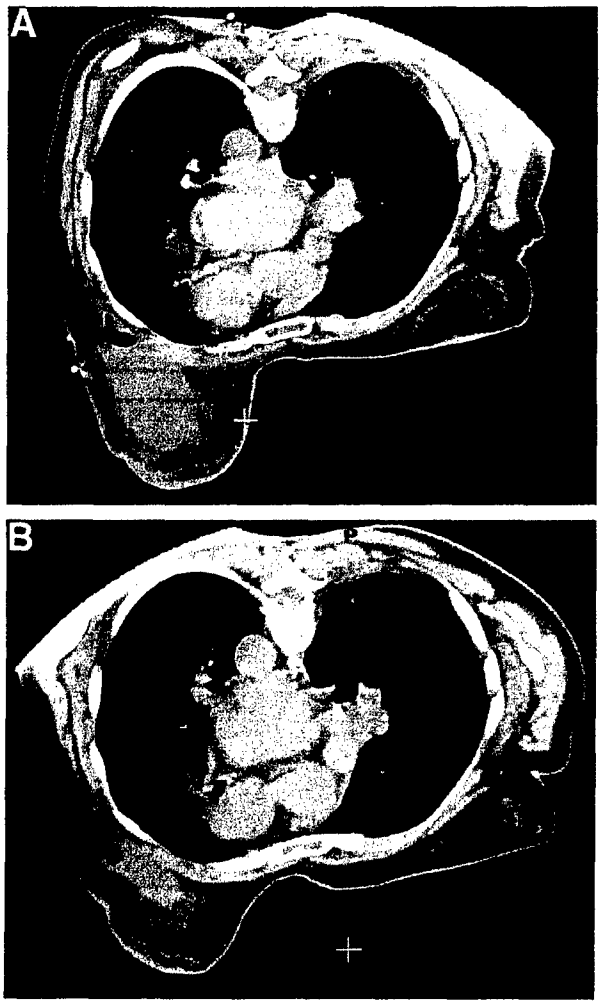

Figure 4 (A) This patient was originally imaged 18 days after segmental mastectomy. When the patient came to start treatment 10 days later (28 days after surgery), it was noted that the ipsilateral breast contour had changed. (B) When imaged again, the postoperative seroma had partially resolved, with absorption of the air present at the first CT, and the contour and size of the breast had also changed. A new treatment plan was developed.

treatment because of the resolution of postoperative changes. For example, Figure 4a shows a patient who, when first simulated, 18 days after surgery, had a large fluid collection with an air level visible on CT. The ipsilateral breast was also enlarged and deformed by postoperative edema. Ten days later, when she came to start treatment (28 days from initial surgery), the size of the breast had decreased, and it also became evident that the excision cavity had changed in size, as confirmed by a new treatment planning CT (Fig. 4B).

Another concern is whether the dose chosen for EB-PBI is adequate for tumor control. We have addressed this issue in a recent manuscript that compares the biological effective doses used in PBI studies to those delivered to the tumor bed by more standard whole-breast regimens of 50 Gy in 5 weeks or whole-breast plus boost regimens of 60 Gy in 6 weeks.[33] It appears that the BED values of most PBI protocols (with either external-beam or brachytherapy techniques) resulted in tumor control BEDs roughly equivalent to a 50 Gy standard treatment but consistently lower than the BEDs for regimens in which the tumor bed receives a total dose of either 60 Gy or 66 Gy. In view of the results of trials demonstrating significantly better local control when a boost is added to the tumor bed,[34,35] future studies of external beam PBI should consider whether a higher dose should be given.

Finally, when large fraction sizes are used, differences in normal-tissue radiosensitivity are likely to be magnified. There are currently no predictive markers to determine which patients will develop radiation-induced late toxicity. Li and colleagues[36] detected a significant correlation between pretreatment plasma levels of tumor growth factor-β-1 (a multifunctional cytokine implicated in tissue fibrosis) and the risk of severe fibrosis among patients treated with breast-conservation therapy. Other studies have revealed that specific polymorphisms of the tumor growth factor-β-1 promoter gene could be associated with the development of severe fibrosis. In 1 study, patients with the −509TT or +869CC genotypes were 7 to 15 times more likely to develop severe fibrosis.[37] Hopefully, studies of "radiation genomics" may result in a panel of markers that can be used to prospectively detect "fibrosis-prone" individuals.

Future Directions

The phase III NSABP/RTOG protocol is described elsewhere in this issue by Vicini and Arthur. Completing this study is critical to establish the role of PBI in the management of patients with early-stage breast cancer. Until then, any form of PBI remains experimental and must be conducted as part of a trial approved by an institutional review board.

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APPENDIX 4

To the Editor: We would like to thank Roques and colleagues for their interest and comments regarding our study. We agree that accuracy is the main priority in immobilization over patient comfort, but this randomized trial failed to show any significant differences in accuracy between the two types of thermoplastic masks studied.

We also agree that a low shoulder position is important in radiation therapy for head-and-neck cancer patients, but we believe that this could be achieved without using a head-shoulder mask (HSM). For instance, a head mask (HM) could be used in combination with a shoulder retractor system (straps with handles fixed to the treatment couch) to achieve a low shoulder position without increasing the risk of severe skin toxicity or claustrophobia.

It may be true that the skin toxicity is high in our study, but regardless of where the World Health Organization (WHO) Grade 3 toxicity occurred, the study shows a statistical significant difference between the HM and the HSM. The highest grade of skin toxicity according to WHO was reported weekly, and even small areas of toxicity (for instance, in skin folds on the neck or behind the ears) were reported. We also would like to point out that the two compared groups of patients (using HM or using HSM) were similar in age, gender, tumor stage and site, type of treatment, beam energy, boost by electrons, and skin types.

We did not find any other studies that focused on the patients' experiences of using immobilization systems and were surprised that more than half (58%) of the patients experienced claustrophobia using the HSM and 45% of the patients using HM. However, all patients in our study were treated by the same specialist-trained cancer nurses with long experience, as suggested by Roques *et al.*, but we could not detect a statistical significant difference between patients using HM and patients using HSM.

The purpose of our study was not to prove which type of fixation is the best on the market. Instead our purpose was to compare the two types of thermoplastic masks that are being used at our department and to find differences that are detectable in a randomized trial.

New fixation devices are developed constantly and will hopefully improve the reproducibility. Some are commercially available and others remain in use locally. The two types of thermoplastic masks compared in our study were those in use clinically at the time of the study (and still with slight alterations). We have failed to find any published data regarding the reproducibility of the vacuum-formed PolyEthleneTerephtalate glycol (PETG) mask in combination with the Norwich head rest, but would be interested to take part of such data if there are any available.

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BIOLOGIC COMPARISONS OF PARTIAL BREAST IRRADIATION SCHEDULES: IN REGARD TO ROSENSTEIN *ET AL.* (*INT J RADIAT ONCOL BIOL PHYS* 2004;60:1391–1404)

To the Editor: In the treatment of breast cancer, many plausible scientific theories have proved illusory when put to the test in clinical trials. The article by Rosenstein *et al.* (1) contains much elegant mathematical and biologic analysis of various radiotherapy schedules used for partial breast irradiation (PBI), as well as an excellent exposition of the rationale for using such techniques, but the conclusions they arrive at on the basis of their calculations are unduly pessimistic, an assertion that has already been shown to be correct in the clinic by the gold standard of a randomized controlled clinical trial. They conclude that, whereas certain PBI schedules are likely to be as effective as a schedule of 50 Gy in 25 fractions, they will be clinically inferior to schedules giving higher doses (60–66 Gy) in fractions of 2 Gy. Correctly interpreted, the available data show that there is minimal clinical benefit in using the higher dose in the sort of patients most likely to be offered PBI.

The European Organization for Research and Treatment of Cancer (EORTC) "boost" trial (2) is widely regarded as justifying the use of these higher doses, but this is a misinterpretation of that pivotal trial, except for certain readily identifiable patients: the younger ones. It is worth reviewing that EORTC trial in some detail. In its design, randomization between treatment arms was stratified for various factors; importantly, patient age at time of entry. The stratification was between those younger or older than 40. (Incidentally, in the original publication, results for those who were older than 40 were presented in three groups, 40–50, 50–60, and older than 60 years, but statistically this lacks validity, because the stratification was simply two-way, so only two groups should have been considered). For the younger patients, whose "baseline" rate of recurrence was much higher, the absolute reduction of risk produced by use of a higher dose was substantial, and clinically as well as statistically significant. For older patients, the absolute gain was minimal, even if statistically significant, because local control in the 50-Gy arm was already excellent. The data clearly show that for those older than 40 years, there is little additional benefit from higher doses, and it is suggestive that the impact of higher dose gets progressively less as patient age increases, but this latter conclusion has to be tempered with caution for the statistical reasons just mentioned.

The most rational interpretation of the EORTC study is that "low-risk" patients gain minimal or no benefit from doses higher than 50 Gy. Age is the most dominant predictor of risk in this trial, and this accords with numerous other studies, but other prognostic features have been widely recognized, such as vascular invasion, lymph node positivity, and extensive intraduct component. The authors refer to a "plateau" effect on the dose–response curve: the evidence from the EORTC trial points to 50 Gy as being very close to such a "plateau" for most older patients. They correctly identify that such patients are the ones most likely to be offered PBI.

It is precisely for these low-risk patients that PBI is seen as an attractive option—and for such patients, 50 Gy should be regarded as the standard comparator among schedules using 2 Gy per fraction. If the biologic calculations of Rosenstein *et al.* are correct, the better PBI schedules will, clinically, be perfectly adequate. Clinical confirmation of this hypothesis is, of course, still awaited.

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IN RESPONSE TO DR. MORGAN

To the Editor: We completely agree with Dr. Morgan's opening statement with regard to the necessity to test any hypothesis or theory in the setting of clinical trials: this is in fact the last sentence in the conclusion of our article (1).

Regarding the correct interpretation of the available data and, in particular, of European Organization for Research and Treatment of Cancer (EORTC) Trial 22881: at the 2004 European Society for Therapeutic Radiology and Oncology (ESTRO) meeting, Antonini *et al.* presented the results on local control and age from the EORTC Trial 22881, with the updated follow-up of 77.5 months (range, 0.53–147.5 months). Quoting from the published abstract: "On the relative hazard scale, there is no evidence that the effect of the boost treatment on local control depends on age ($p = 0.871$)" (2). Regarding the correct interpretation of our conclusions: we stress the importance of patient selection for partial breast irradiation (PBI), a point we have made before (3–5). Accrual to our current trial of prone PBI is limited to selected postmenopausal women who are treated by 30 Gy in five fractions. In fact, we have hypothesized that such a dose could be sufficient in this population. As stated in the recent manuscript about this trial, "whether the hypofractionated regimen (30 Gy in five fractions within 10 days) will be revealed as adequate in ensuring tumor control in the carefully selected population studied in this trial warrants long-term follow-up" (4).

Through radiobiologic modeling, we wanted to stress the difference between currently used PBI regimens and standard whole-breast radiotherapy, a relevant exercise in view of the fact that many current PBI trials are offered to women of any age, with the same potentially insufficient dose.

Standard adjuvant whole-breast radiotherapy is a highly effective component of breast conservation: "lesser" regimens require cautious explora-

tion, including initial patient selection criteria that reflect what we already know. Ignoring heterogeneity of breast cancer and its distinct natural history in different age groups, including patterns of local recurrence, is unlikely to foster progress in this field.

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MINIMIZING URINARY BLADDER RADIATION DOSE DURING BRACHYTHERAPY FOR CARCINOMA OF THE CERVIX USING BALLOON INFLATION TECHNIQUE: IN REGARD TO MALAKER *ET AL.* (*INT J RADIAT ONCOL BIOL PHYS* 2005;61:257–266)

To the Editor: It was with great personal interest that we read the article by Malaker *et al.* (1) on the reduction of bladder radiation dose during brachytherapy for cervical cancer using balloon inflation technique. With extensive experience using balloon catheters to minimize bladder *and* rectal dose during gynecologic brachytherapy at our institution, we have incorporated the balloon catheter technique as a standard of care and have written extensively on this subject (2, 3). It was thus with surprise that we found no references to the work we have already done in the very journal that Malaker's article is printed. Perhaps this oversight is also shared partially by the reviewers.

In addition, there are some technical issues we would like to point out. Figure 2 of the article shows lateral simulation films of the uterine applicators *in situ*, in which the tandem is clearly placed too anteriorly in relation to the ovoids. Although the purpose of the film is to show the displacement of the bladder that can be achieved by inflating the balloon catheter, we also advocate correct placement of the applicators, especially in a published article.

It is also apparent from these simulation films that no internal shields were used with the ovoid applicators. Using such shields is a practice standard at our institution and the lack of such shields may have very well skewed the bladder (and rectal) exposure.

Next, the use of the distal opening of the catheter as an anchor to the tandem, though resourceful, does not take into account variations seen in patient anatomy, particularly location of the bladder. Some bladders sit more cephalad, others more caudal. In our institution, adjustments often have to be made in the placement of the balloon catheter if the bladder does not sit directly above the balloon. This involves deflating the balloon, making the adjustment, then reinflating the balloon with another simulation film taken. Therefore, the authors' technique may not be practical for all patients.

In summary, the authors' findings only served to confirm what we have already demonstrated—that balloon catheters can reduce unnecessary dose to the bladder, although we have conclusively shown that rectal dose can also be reduced (2). Nevertheless, we are happy to learn of the authors' use of the balloon inflation technique and look forward to seeing the use of balloon catheters incorporated as a standard of care in more centers besides our own.

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IN RESPONSE TO DR. LUH *ET AL.*

To the Editor: For potential users of the balloon inflation technique for cancer of cervix, we would like to respond to the issues raised by Luh and Eng to inform practicing colleagues. We were happy to learn of the adoption elsewhere of a balloon inflation technique for treatment of cancer of the cervix, a technique that we previously described in our widely internationally circulated Annual Report of 2002 (1), a copy of which is available on request. After submission of our article to this journal in August 2003 (2), we subsequently learned of its application at the University of Texas Health Science Center at San Antonio after publication of an article by Eng *et al.* (3) in May 2004.

Regarding the anterior placement of the tandem, Fig. 2 in our original article was included as an example to demonstrate that, even when it is markedly anteriorly placed, the dose to the bladder is reduced by increasing the separation between the tandem and the bladder. Second, spherical ovoids tend to hold the tandem on their curved surfaces as they meet together; as a result, the tandem is pushed upward. However, if cylindrical ovoids are used, the tandem will lie in the middle of the ovoids; this is the system we usually use. Consequently, if the patient has posterior packing behind the tandem in the gap between the two ovoids, it holds the lower end of the applicator system and, if the packing is done satisfactorily, this would not be a practical problem in performing this procedure.

It should also be noted that by lifting the vaginal portion of the applicator, it acts as a retractor, and posterior packing becomes relatively easy. In this case, posterior packing can be done well under direct vision and posterior displacement of the rectum can be assured, thus helping to reduce the rectal dose.

Shielded ovoids can be employed, but the BrachyVision computer calculation system we use does not allow for a shielded applicator (4). Any shielding correction would have to be applied to the results determined by the BrachyVision system by a physicist, but the perturbation effect of the shielding cannot readily be calculated, nor is there a program available to our knowledge to incorporate a shielding correction into the calculation module. Consequently, although in principle it may be a good idea because we do not have an accurate method of calculation, we have chosen to employ the approach of increasing the distance to the rectum by packing and to use an accurate method of calculation rather than using less packing and a dose approximation.

With regard to the distal opening of the catheter, it must be used as an anchor to the tandem to make it secure against slipping, because, if the packing is not done with care, when the balloon is inflated, it can slip backward and between the ovoids or sideways, defeating the whole purpose of the exercise.

Novel Approaches to Postoperative Radiation Therapy as Part of Breast-Conserving Therapy for Early-Stage Breast Cancer

Minh Tam Truong, Ariel E. Hirsch, Silvia C. Formenti

Abstract

Breast-conserving therapy (BCT) consists of segmental mastectomy followed by postoperative radiation therapy (RT) to the whole breast. At least 6 prospective randomized trials have proven the equivalence of BCT to mastectomy. However, BCT remains underused and, most importantly, a sizable proportion of patients with invasive breast cancer fail to complete the recommended protocol of breast preservation by omitting postoperative RT. The inconvenience of complying with the standard 6-week radiation regimen, which includes approximately 30 daily visits, at least partially explains this lack of adherence. New clinical studies have generated preliminary evidence that more convenient, shorter radiation regimens might reveal equivalence to the current standard. Moreover, the availability of modern technology to deliver and target ionizing radiation by improving homogeneity of radiation dose has made it possible to safely explore the use of greater radiation doses per fraction. Finally, currently ongoing research trials will enable the identification of specific subsets of patients who are likely to be safely treated by partial-breast radiation (instead of radiation to the whole breast) with more accelerated regimens. This article reviews the available data and the current ongoing research on novel RT techniques and fractionation schedules in BCT for early-stage breast cancer.

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Breast-Conserving Therapy

At least 6 prospective, randomized controlled trials have demonstrated the equivalence of breast-conserving therapy (BCT) to mastectomy.[1-6] Despite level 1 evidence of comparable efficacy to that of mastectomy, BCT remains underused in the United States.[7-12] In 1990, the National Institutes of Health (NIH) Consensus Development Conference concluded that BCT was the appropriate method of treatment for the majority of women with early stage I or II breast cancer.[13] However, this subsequently translated to only a moderate increase in the use of BCT, from 34% to 60% for stage I breast cancer and from 19% to 39% for stage II breast cancer.[14] There appear to be multiple causes for the underuse. The demands of the standard radiation schedule and its perception by referring surgeons and patients probably play a role.

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Generally, radiation therapy (RT) after lumpectomy consists of 4-5 weeks of whole-breast radiation of a total dose of 45-50 Gy in 23-25 fractions, usually followed by a boost of 10-16 Gy in 5-8 fractions to the tumor bed area (Figure 1). The total length of treatment is 5-7 weeks, commonly 6 weeks. Thus, women who choose BCT automatically commit to a regimen of approximately 6 weeks of daily radiation treatments (Monday through Friday) to complete the local management of their breast cancer. For many women, concerns about this commitment are likely to influence the choice for mastectomy instead of breast preservation: only 40%-60% of women who meet criteria for BCT actually undergo the procedure.[14] Studies that have addressed the components of the decision-making choices in women choosing mastectomy suggest that the inconvenience of RT is a factor influencing their decision; concerns arise about the inconvenience, duration of treatment, and travel restrictions associated with the radiation component of breast preservation. The surgeon or primary health care provider also appears to be influential in the process.[15] As a consequence, some surgeons use more stringent criteria than those in published guidelines and recommend mastectomy to their patients based on the perceived difficulties of adhering to a 6-week postoperative regimen.[7] An example of BCT underuse comes from the Arimidex, Tamoxifen, Alone or in Combination trial, in which higher rates

of mastectomy for women who would have otherwise been eligible for BCT had occurred in the United States than in other countries.[16]

In addition to the effect of possible biases of the primary health care provider, distance from RT treatment facilities has also been shown to correlate with patient choice to undergo mastectomy instead of BCT.[17-21] Most importantly, 15%-30% of patients who have actually selected BCT, particularly older patients and those with ≥ 2 comorbid conditions, do not receive postoperative RT.[17,18,22-26] These facts warrant a critical assessment of standard RT and justify the exploration of new radiation regimens.

Radiation Therapy in Breast-Conserving Therapy

Several multivariate analyses have found no patient subgroup with sufficiently low risk of in-breast recurrence (IBR) to avoid treatment with whole-breast external-beam RT as part of the breast-conserving management of breast cancer.[27-29] As a consequence, the last NIH Consensus Statement on this subject (2000) maintained the standard of care for BCT as breast-conserving surgery followed by whole-breast external-beam RT.[30]

Data from pathologic studies justify this recommendation. For instance, in a study of 135 mastectomy specimens of breast cancer from patients theoretically eligible for conservative treatment (≤ 4 cm in size, all pathologic types except invasive lobular carcinoma), it was found that, even with ≥ 1 cm free of tumor beyond the dominant mass, in 11% of cases, tumor was found in the breast beyond 2 cm of distance, thus arguing that surgery alone may not be sufficient.[31]

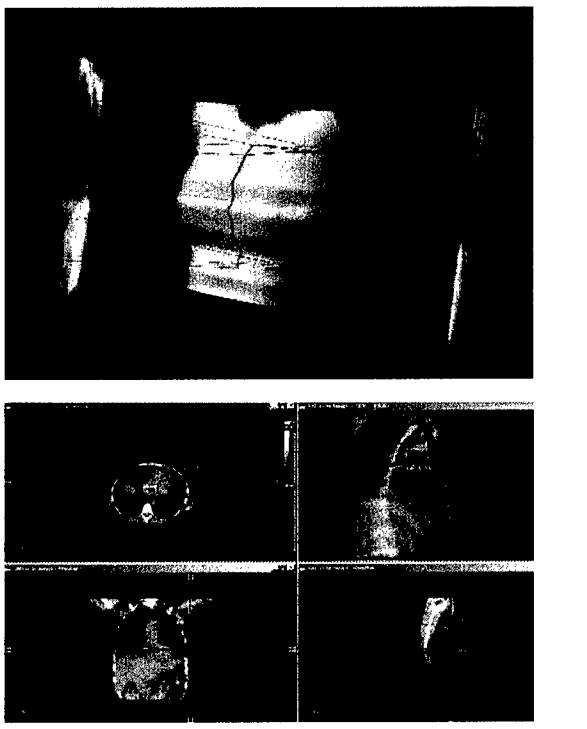
Similar clinical data are available to demonstrate unacceptable risk of recurrence if radiation is omitted. Illustrating this is the experience of the Joint Center for Radiation Therapy in a study that omitted the use of adjuvant radiation after wide excision alone in T1 tumors (median tumor size, 0.9 cm).[32] Eligibility criteria limited study inclusion to carriers of unicentric T1 infiltrating ductal, mucinous, or tubular cancers without extensive intraductal component (EIC) or lymphatic vessel invasion; negative margins of excision measuring ≥ 1 cm; and negative axillary nodes. Despite the stringent eligibility criteria and the fact that 75% of the lesions were mammographically detected (nonpalpable), the study was discontinued prematurely because of unacceptable local recurrence rate: 16% at 56 months of follow-up, or a 3.6% annual rate of local recurrence. The authors concluded that, even in a stringently selected group of patients with early-stage breast cancer, a considerable risk of local recurrence persists after conservative surgery without radiation. Interestingly, most recurrences were at the original tumor site, confirming that the original tumor bed remains the area at the highest risk for recurrence after surgery.

Omission of Radiation Therapy After Quadrantectomy

Recent evidence has emerged that performance of quadrantectomy—a more generous surgical excision than segmental mastectomy, equivalent to a quadrant of the breast—may allow omission of radiation in a selected subset of patients. In a retrospective study of 356 patients > 60 years of age with stage I or II breast cancer treated by quadrantectomy and axillary dissection, the subset of patients with negative lymph nodes and positive receptor status had a locoregional recurrence rate of 3% (median follow-up of 60 months) with or without adjuvant radiation.[33] These findings were confirmed by the results of the Milan III trial, a randomized trial testing the effect of radiation after quadrantectomy.[34] This trial demonstrated that, for women treated by quadrantectomy, as the age of the patient increased, the risk of local recurrence decreased. The difference in the risk for ipsilateral breast recurrence appeared to be particularly high in women ≤ 45 years of age and then tended to decrease with increasing age, with no apparent difference in women > 65 years of age.

In fact, for women ≥ 66 years of age, the local recurrence rate was 4% with or without RT, whereas women < 45 years of age had local recurrence rates of 43% with surgery alone and 9% with surgery and RT. In the group aged 46-55 years, the local recurrence rates were 20.2% without RT versus 5% with RT. In the subset of women aged 56-65 years, the risk was 12.1% without RT versus 2.4% with RT. The authors concluded that women ≤ 55 years of age derive a significant benefit from whole-breast postoperative radiation when quadrantectomy is performed. For women > 65 years of age, quadrantectomy alone is probably adequate.[34]

Figure 1 Digital Reconstruction and Computed Tomography Planning for External-Beam Radiation



(A) Digital reconstruction of a patient's body and projection of tangent beams on the skin surface. **(B)** CT planning for external-beam radiation of a patient in supine position. The normal tissue structures including lung and heart, and tumor and the tangent field are outlined on the digital reconsructed radiograph (top right), axial plane of tangent fields (top left), coronal plane (bottom left), and sagittal plane (bottom right).
Abbreviation: CT = computed tomography

Table 1 Actuarial Results of NSABP B-21 Trial

Treatment	Median Follow-up (Months)	Number of Patients	5-Year IBR	8-Year IBR
Surgery + Tamoxifen + Radiation	87	334	2%	2.8%
Surgery + Placebo + Radiation	86	332	4%	9.3%
Surgery + Tamoxifen	89	334	10.5%	16.5%

Abbreviations: IBR = in-breast recurrence; NSABP = National Surgical Adjuvant Breast and Bowel Project

In North America, quadrantectomy is not commonly performed, and according to a retrospective study of McCready et al, may translate to patients treated with segmental mastectomy or lumpectomy.[35] Local failure rate was 9% at 10 years after lumpectomy alone among patients who were ≥ 65 years of age and had favorable pathologic features including negative nodes, no comedo features, no lymphovascular invasion, and estrogen receptor–positive tumors.

Omission of Radiation Therapy After Segmental Masectomy

The identification of a distinct subset of women who could be safely treated by segmental mastectomy without the addition of RT was the motivation for 2 prospective randomized trials in older women that further addressed the issue of omitting RT in elderly patients. A Canadian randomized trial of women > 50 years of age with T1 or T2 node-negative breast cancer compared tamoxifen alone to tamoxifen and RT.[36] With a median follow-up of 3.4 years among 769 patients (83% with T1 breast cancer), the relapse-free rate in the ipsilateral breast was 94% in the tamoxifen-alone arm, compared with 99.7% in the tamoxifen/RT arm ($P = 0.0009$).

An Intergroup trial conducted by Cancer and Leukemia Group B randomized 647 postmenopausal women ≥ 70 years of age with stage I estrogen receptor–positive breast cancer to tamoxifen versus tamoxifen and RT. With a short follow-up of 28 months, the rate of locoregional failure was very low, 0.9% annually (6 of 319 recurrences in the tamoxifen-alone arm and none in the tamoxifen/RT arm; P value not significant). This study suggests that the benefit derived from RT in this elderly group of patients is very limited as a result of the high incidence of death from other causes. The rate of breast recurrence in the index breast was actually similar to the rate in the contralateral breast.[37]

Could an original tumor size of ≤ 1 cm justify the avoidance of postoperative RT? This was investigated by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-21 trial, which was limited to women with invasive breast tumors ≤ 1 cm in largest dimension, who had undergone lumpectomy with tumor-free margins at pathology, and who had axillary dissection with negative lymph nodes. Approximately 80% of the women in the NSABP 21 trial were ≥ 50 years of age and 76% of women were postmenopausal.[38] The cumulative incidence of IBR at 8 years was 16.5% with tamoxifen alone, 9.3% with RT and placebo, and 2.8% with the combination of tamoxifen and RT. Distant treatment failures were infrequent and not significantly different among groups ($P = 0.28$). Survival rates in the 3 groups were 93%, 94%, and 93%, respectively ($P = 0.93$). Although NSABP B-21 trial showed that whole-breast external-beam RT significantly reduced the actuarial estimate of incidence of IBR at 8 years, it also demonstrated that IBR continued to occur with time, as demonstrated by the gradual increases at 5 and 8 years of follow-up (Table 1). Protracted observation time to assess IBR is warranted, even in a population of patients with very small primary breast cancers.

Patterns of Local Recurrence After Breast-Conserving Therapy

Results from 5 prospective randomized trials of breast-preserving surgery with or without adjuvant RT have elucidated the geographic patterns of local recurrence after lumpectomy alone and thereby provide the foundation to justify the exploration of partial-breast irradiation (PBI)[2,28,29,38-40] (Table 2[1,2,28,29,40]). In each of these trials, most failures occurred in the tumor bed, raising questions as to the necessity of irradiating the whole breast. For instance, in the NSABP B-06 trial, all recurrences were reported to be within or close to the quadrant of the original tumor.[41] In the study of Liljegren et al, in a more select group than patients from NSABP B-06, 381 patients with unifocal T1 breast cancers (premenopausal and postmenopausal women) were randomized to sector resection with or without radiation.[29,42] Predictably, at 10-year follow-up, significantly higher rates of local recurrences occurred in the arm of patients who underwent segmental mastectomy alone compared with the arm of patients who underwent segmental mastectomy and postoperative RT (24% vs. 8.5% at 10 years). Noticeably, 67% of the recurrences in the surgery-alone arm occurred within the initial tumor bed. A similar geographic pattern of local recurrence has also been demonstrated in other studies.[43,44] The study of Veronesi

Table 2 Prospective Randomized Trials of Breast-Preserving Surgery with or Without Adjuvant RT

Study	Number of Patients	Cancer Size (cm)	Type of Surgery	Local Recurrence with Surgery Alone	Local Recurrence with Surgery + RT	Follow-up (Years)
Fisher et al[1]	1362	4	WE	39%	14%	20
Veronesi et al[2]	567	4	Q	8.8%	2.3%	20
Clark et al[28]	837	4	WE	35%	11%	7.6
Liljegren et al[29]	381	2	SR	24%	8.5%	10
Forrest et al[40]	585	4	WE	24.5%	5.8%	6

Abbreviations: IBR = in-breast recurrence; Q = quadrantectomy; RT = radiation therapy; SR = sector resection; WE = wide excision

et al, which included a more generous surgical operation, a quadrantectomy, had the lowest local recurrence rate, suggesting that surgical removal of more tissue adjacent to the tumor favorably affects local control.[45]

In these randomized trials, the arm of patients who did not undergo RT to the whole breast consistently showed higher recurrence rates and a pattern of recurrences that occurred mostly in the tumor bed. These findings question whether irradiation to the whole breast is necessary and have opened the opportunity to investigate PBI in selected patients with breast cancer treated by BCT.

Challenging the Current Standards for Volume and Dose Fractionation of Breast Irradiation

Although it is clear that the exploration of shorter treatment regimens is warranted, especially in view of the fact that new technology has made it possible to homogeneously deliver radiation treatment while better sparing normal tissue, the optimal fractionation regimen for postoperative breast RT has yet to be defined.

Whole-Breast Radiation: Accelerated Fractionation Regimens

Hypofractionated Accelerated Regimens. Hypofractionation (the delivery of dose fractions substantially larger than the conventional 2 Gy) for breast cancer treatment was common in the 1940s and 1950s and, even though successful in achieving tumor control, was found to leave significantly inferior cosmetic results as a result of severe fibrosis and telangiectasia.[46,47] These late complications resulted from the use of very large fields that included a large proportion of uninvolved skin and tissue surrounding the tumor. Already in 1949, Baclesse had discovered the therapeutic ratio was largely dependent on the field size.[48] He advocated the use of a "sufficient number of contiguous small fields in rotation" as the future for breast cancer RT.

Baillet et al conducted the first prospective randomized trial studying hypofractionated radiation.[49] Patients were randomized to receive either "classical" RT consisting of 45 Gy in 25 fractions over 33 days or hypofractionated radiation consisting of 23 Gy in 4 fractions over 17 days. The first 230 patients randomized were followed for a minimum of 4 years. The 5-year actuarial survival was identical in the 2 arms. The local recurrence rates were 7% (9 of 125) in the hypofractionated radiation group and 5% (5 of 105) in the classical RT group, with no significant difference in local control between treatment arms. The study also detailed complications of each treatment groups including arm lymphedema, fibrosis, and telangiectasia. No statistical difference in the overall rate of complications between the treatment groups was noticed: 23% hypofractionated group versus 19% in the classical group.

Among a number of retrospective reports on shorter whole-breast radiation fractionation schemes, perhaps the most relevant is by Olivotto et al.[50] The regimen used a dose of 44 Gy in 16 fractions in 22 days via tangential fields to the whole breast of 186 women with T1 or T2 pathologically node-negative breast cancer. The 5-year actuarial recurrence rate was 6%, which was comparable with other studies of conventional fractionation (over 6 weeks). Additionally, evaluations of the cosmetic scores were good or excellent in 89% and 96% of cases according to physicians and patients, respectively. Thirteen percent of patients reported mild inframammary telangiectasia at 5-year follow-up.

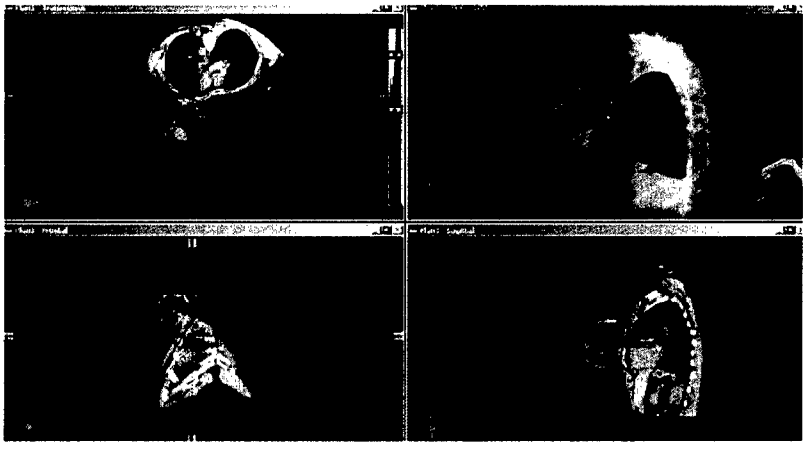
A Canadian retrospective review of a shorter radiation schedule used in patients with breast cancer after lumpectomy provided the preliminary evidence to further explore that hypofractionation schedule.[51] A total of 298 patients were treated with 40 Gy in 16 fractions at 2.5 Gy per day with opposed tangent fields. Median follow-up for this series was 5.5 years. The 5-year actuarial relapse rate was 3.5%, with overall 5-year survival and disease-specific survival rates of 87.8% and 92.1%, respectively. These results were comparable with those derived from historical controls. The regimen appeared sufficiently safe and effective to be prospectively tested in a subsequent phase III trial.

The controlled randomized trial of Whelan et al compared 2 radiation schedules after lumpectomy in women with lymph-node negative breast cancer.[52] The trial included women with T1/2 N0 tumors that were completely excised with negative margins. Between 1993 and 1996, 1234 women were randomly assigned to either the "long" arm of 50 Gy in 25 fractions over 35 days or the "short" arm of 42.5 Gy in 16 fractions over 22 days (2.65 Gy per day). The primary endpoint was the assessment of local control in the treated breast. There were a number of exclusion criteria including breast size (distance of separation ≥ 25 cm), lack of levels 1 and 2 lymph node dissection, and positive margins. At a median follow-up of 69 months, the 5-year local recurrence–free survival rates were 97.2% in the short-RT arm and 96.8% in the long-RT arm. Overall and disease-free survival rates were also equivalent. The incidence of late skin toxicity was low in both arms, with comparable cosmetic outcome. Specifically, the percentages of patients with an excellent or good global cosmetic outcome at 3 years were 76.8% in the short-RT arm and 77.0% in the long-RT arm; the corresponding data at 5 years were 76.8% and 77.4%, respectively. Although this trial represents an important milestone in the investigation of modern RT in breast cancer, more work needs to be done, for instance, to explore how to integrate a boost to the tumor bed in accelerated whole-breast radiation or how to develop a technique that does not exclude patients with large breasts.

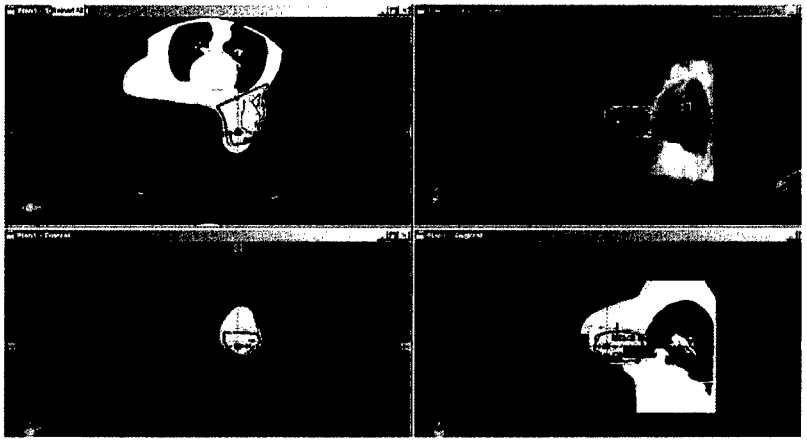
Hypofractionated Nonaccelerated Regimens. In another randomized trial, between 1986 and 1998, 1410 patients with early-stage invasive breast cancer were randomized to 3 different dose fractionation schedules, all delivered over a period of 5 weeks. Of note, although the trial tested hypofractionation, it did not accelerate treatment; rather, overall treatment time remained the same (5 weeks). The 3 schedules were 50 Gy in 25 fractions daily over 5 weeks (2 Gy per fraction), 39 Gy in 13 fractions (3 Gy per fraction), and 42.9 Gy in 13 fractions (3.3 Gy per fraction). The latter 2 schedules are delivered on Monday, Wednesday, Friday, Tuesday, Thursday, etc, 5 times every 2 weeks. Only initial cosmetic results have been reported,[53] and the trial has now been incorporated into the UK Coordinating Committee on Cancer Research breast RT fractionation trial, the Standardization of Breast Radiotherapy Trial, which was closed to accrual in September 2002.

Figure 2 Digital Reconstruction and Computed Tomography Planning in a Prone Position

A Whole-Breast Radiation



B Partial-Breast Radiation



Intensity-Modulated Radiation Therapy

Intensity-modulated RT (IMRT) uses a sophisticated computer-controlled radiation beam delivery method to improve the conformation of the dose distribution to the shape of the tumor. This is achieved with variation of the radiation intensity within each beam, as opposed to the uniform beam intensities used by 3-dimensional (3D) conformal RT. Intensity-modulated RT usually incorporates inverse treatment planning, whereby the user initially specifies the organ dose limits and the desired doses to the target tissues. The computer then generates an optimal plan then adheres to the dose limits specified.

To improve upon the dose delivery achieved by 3D conformal RT using breast wedged tangents, IMRT has been applied to breast RT. Intensity-modulated RT aims to improve the dose to all critical normal tissue structures including the heart and lungs. While current studies of IMRT applied to breast radiotherapy have shown its feasibility,[54-59] long-term data has yet to determine whether this technique translates to an improvement in the late toxicity profile and cosmesis.

Volume-based IMRT first requires outlining the volumes of interest (target and critical organs) and uses specialized computer treatment planning algorithms to generate a plan that optimally balances the conflicting dose constraints to the target and critical organs. The drawbacks of volume-based IMRT are the increased length of time to deliver the treatment and the labor-intensive dosimetric planning, making it difficult to translate IMRT to a large-scale implementation.[54] However, recent studies have shown that more simplified techniques have evolved.[55,56] Chui et al described a practical and simplified technique of delivering IMRT,[55] which requires significantly less "beam-on" time and dosimetric planning than full-fledged volume-based IMRT, which Hong et al originally described.[54] The technique still achieves the desired dose homogeneity when compared with conventional tangents.

Lief et al explored the potential application of IMRT to accelerated breast RT with patients treated in a prone position.[60] This technique involves prescribing a homogeneous dose to the whole breast while a higher dose is delivered to the tumor bed, thereby delivering the equivalent of a concomitant boost (Figure 2A).

Partial-Breast Irradiation

Treatment Volume: Rationale for Partial-Breast Irradiation

Partial-breast irradiation is generally administered to the portion of the breast that includes the tumor bed, plus a surrounding margin. The advantage of PBI is that, by limiting the volume treated, it is theoretically possible to increase the dose per fraction and safely accelerate dose fractionation, allowing patients to undergo a more convenient and possibly more economical radiation regimen as part of BCT. The cost depends on the procedure used. External-beam (3D conformal) accelerated RT costs less because of the decreased number of fractions compared with the standard regimen (5 vs. 30). Conversely, the use of IMRT is likely to increase cost compared with standard tangent treatment. Similarly, PBI delivered by brachytherapy is likely to be more expensive given the costs associated with operating room time, anesthesia, specialized instrumentation, and radiation sources.

Identification of patients who should be excluded from the accrual to these PBI trials because they are likely to either be insufficiently treated by accelerated PBI or are more likely to develop complications when exposed to larger doses per fraction is rapidly evolving. For instance, Holland et al found that tumors associated with EIC were more likely to have carcinoma in the remaining breast than tumors without EIC (74% vs. 42%; $P = 0.00001$), suggesting a role for whole-breast radiation when EIC is present in view of a large subclinical burden in the remaining breast.[61] Another factor

predicting a higher risk of recurrence includes the presence of involved margins of excision.[62,63] Carriers of tumors that lack these features are likely to be better candidates for accelerated PBI trials.

Partial-Breast Radiation Procedures

Currently, the main available methods of delivering PBI are brachytherapy with ≥ 2 plane implants, use of the MammoSite® device, or external-beam radiation with use of 3D conformal RT, IMRT, intraoperative electron beam RT, or stereotactic radiosurgery.

Brachytherapy Techniques. When brachytherapy is used, radiation can be delivered either at a low dose rate (LDR) over 4-5 days or at a high dose rate (HDR) with 8-10 large fractions. The target volume is the tumor bed with margins. Advantages are the established role of brachytherapy techniques and shortened overall treatment time compared with standard 6-week external-beam radiation. The disadvantages are the need for an invasive surgical procedure, the dependence on skills and experience of the radiation oncologist performing the procedure, and the risk of complications derived from dose inhomogeneity within the target volume. Although the results of the initial brachytherapy experience were disappointing, more recent studies with careful quality assurance and accurate patient selection have led to excellent local control rates with these techniques.

A trial by Fentiman et al investigated LDR brachytherapy to a total dose of 55 Gy with use of Iridium 192 and reported an unacceptably high breast recurrence rate of 37% (10 of 27 patients) at a median follow-up of 6 years.[64,65] The investigators attributed the high local recurrence rate to the disproportionate inclusion in this series of younger women with unfavorable tumor characteristics, including median tumor diameter of 3.5 cm in the relapse group, and the presence of lymphovascular invasion, necrosis, positive margins, and involved axillary nodes. Moreover, most women received possibly inadequate implants, with a median number of 9 catheters resulting in treatment to the target volume with insufficient margins.

In a study by Clark et al, HDR brachytherapy delivering a total dose 20-32 Gy was used.[66] The local failure rate was 15.5% (7 of 45 patients) at 18 months.

King et al conducted a prospective phase I/II study of wide-field brachytherapy after segmental mastectomy for selected patients with breast cancer with intraductal or invasive tumors ≤ 4 cm in size, negative inked surgical margins, and ≤ 3 positive axillary nodes using wide-field double-plane ^{192}I brachytherapy implants.[67] Alternating consecutive cohorts of 10 patients were assigned to receive either continuous LDR brachytherapy of 45 Gy to the target volume over 4 days or fractionated HDR brachytherapy of 32 Gy in 8 fractions of 4 Gy each, given twice a day (b.i.d.) over 4 days. A matched-pair analysis with 94 patients who would have met the eligibility criteria for the study but were treated with conventional external-beam RT during the same time period was performed. With a median follow-up of 75 months, the locoregional recurrence rate was 8% (1 breast recurrence and 3 regional nodal recurrences among 51 cases) in the brachytherapy group, compared with 5% in the external-beam RT group (*P* value not significant).

Similar results were reported by Vicini et al, who conducted a retrospective matched-pair analysis of 174 patients with stage I/II infiltrating ductal carcinoma with tumors < 3 cm, negative EIC, negative surgical margins, and < 3 lymph nodes involved.[68] One hundred twenty patients (69%) underwent LDR brachytherapy (50 Gy over 96 hours) and 54 patients (31%) underwent HDR brachytherapy (46 patients received 32 Gy in 8 fractions 6 hours apart and 8 patients received 34 Gy in 10 fractions 6 hours apart). Fifty-two percent of the patients received adjuvant tamoxifen and 11% received adjuvant systemic chemotherapy. At a median follow-up of 36 months, there were no statistically significant differences in the 5-year actuarial rates of ipsilateral breast or locoregional recurrences and no differences in disease-free or overall survival.

Perera et al reported a pilot study of 39 patients who underwent HDR brachytherapy.[69] At a median follow-up of 20 months, 1 local recurrence was reported. Complications of treatment included fat necrosis in 4 patients (10.3%) at the lumpectomy site at 4, 13, and 18 months after implantation.

At a multiinstitutional level, the first preliminary report of Radiation Therapy Oncology Group (RTOG) 95-17 shows promising results.[70] RTOG 95-17 is a phase I/II multiinstitutional trial investigating brachytherapy alone after lumpectomy in 100 patients with tumors ≤ 3 cm excised with inked negative margins. Exclusion criteria were lobular histology, presence of EIC, and ≥ 4 involved nodes. Thirty-three patients were treated with LDR brachytherapy (45 Gy over 3-5 days) and 66 patients were treated with HDR brachytherapy (34 Gy in 10 b.i.d. fractions over 5 days). The target volume was defined as 2 cm beyond the lumpectomy cavity peripherally and 1 cm superficial and deep. At a median follow-up of 2.7 years (0.6-4.4 years), the incidences of grade III toxicity were 9% in LDR-treated patients and 2% in HDR-treated patients. It was noted that patients who received chemotherapy had a substantially increased risk of complications compared with patients who did not: 55% with LDR brachytherapy and 14% with HDR brachytherapy. Among patients who did not undergo chemotherapy, grade III toxicity occurred in no patients receiving LDR brachytherapy and 4% of patients in the HDR brachytherapy group. Furthermore, acute toxicities related to the surgical procedure in addition to radiation toxicity included breast edema, hematoma, arm edema cellulitis, skin necrosis, abscess formation, wound dehiscence, and breast distortion.[70]

Wazer et al described clinically evident fat necrosis after HDR brachytherapy alone using remote afterloading in 8 of 30 patients (27%) at a median of 7.5 months after the procedure.[71,72] The incidence of fat necrosis appeared to be related to the increased number of source dwell positions and the volume of implant receiving fractional doses of 340, 510, and 680 cGy. A dose–volume effect was shown such that use of implants of larger volume necessitated lowering the fractional dose in order to minimize the risk of late complications. This emphasizes the importance of the volume of tissue being irradiated and its consequences on the probability of complications.

Keisch et al recently reported the multicenter preliminary experience in 54 patients who were implanted with the MammoSite balloon breast brachytherapy applicator.[73] The reason to investigate this device is its potential to be a more

Table 3 Results of Sole LDR and HDR Brachytherapy to the Tumor Bed

Study	No. of Patients	Median Follow-up (Months)	Dose Fractionation	Total Dose (Gy)	Local Recurrence Rate	Good to Excellent Cosmetic Result
HDR Brachytherapy						
Clark et al[66]	45	18	10 Gy × 2 7 Gy × 4 6 Gy × 6	20 28 36	15.5%	95%
King et al[67]	26	75*	4 Gy × 8	32	2%*	75%*
Vicini et al[68]	46 8	36*	4 Gy × 8 3.4 Gy × 10	32 34	0	80%*
Perera et al[69]	39	20	3.72 Gy × 10	37.2	2.6%	–
Kuske et al[70]	66	32*	3.4 Gy × 10	34	–	–
Wazer et al[72]	32	33	3.4 Gy × 10	34	3%	75%
Keisch et al[73]	43	1	3.4 Gy × 10	34	–	88%
Polgar et al (Phase II)[75]	8 37	57	4.33 Gy × 7 5.2 Gy × 7	30.3 36.4	4.4%	97.8%
Polgar et al (Phase III)[75]	63	30	5.2 Gy × 7	36.4	0	–
LDR Brachytherapy						
Fentiman et al[65]	27	72	45 cGy/hour	55	37%	83%
King et al[67]	27	75*	40 cGy/hour	55	2%*	75%*
Vicini et al[68]	120	36*	52 cGy/hour	50	0	80%*
Kuske et al[70]	33	32*	45 cGy/hour	45	–	–

*LDR and HDR combined.
Abbreviations: HDR = high dose rate; LDR = low dose rate

reproducible method of breast brachytherapy that is less dependent on the surgical implant technique. This prospective pilot study tested the use of the MammoSite balloon breast applicator using ^{192}I HDR brachytherapy as a sole radiation modality after lumpectomy in women > 45 years of age with stage I breast cancers with negative pathologic margins. The study design consisted of a total dose of 34 Gy, delivered in 10 fractions b.i.d. for 5 days, prescribed to 1 cm from the applicator surface. Only 43 of the 54 patients were found to be eligible for this technique. MammoSite balloon delivery was not feasible in cases of inadequate balloon-to-skin distance, excessive surgical cavity size, poor balloon conformance, or poor skin-to-device spacing. Complications included seromas (3 of 43) and abscess formation (1 of 43). Dose–volume histogram (DVH) analysis of the MammoSite device appeared to compare its use favorably with catheter-based breast brachytherapy. Generally, the MammoSite device treated a larger volume than its interstitial brachytherapy counterparts. The investigators hypothesized that by following the dose–volume cutoffs, fat necrosis would be unlikely to occur, but this prediction warrants further clinical confirmation.

There have been a number of phase I/II trials of brachytherapy as the sole radiation modality to the breast.[69,72,74] Polgar et al reported the first randomized phase III trial of sole HDR brachytherapy compared with whole-breast RT, with a median follow-up of 30 months.[75] Eligible patients were those with unifocal tumors of stage pT1 N0 or pN0-1a. Pure ductal or lobular pT1s tumors, invasive lobular tumors, and presence of EIC were criteria for exclusion. Initially, 45 patients were enrolled onto a phase I/II study of brachytherapy alone with use of interstitial HDR implants consisting of 7 fractions of 4.33 Gy (n = 8) and 7 fractions of 5.2 Gy (n = 37) delivered to the tumor bed. Based on the results of the initial phase I and II study, 126 patients were further randomized to receive 50 Gy whole-breast RT (n = 63) or brachytherapy alone (n = 63). The dose regimen consisted of either 7 fractions of 5.2 Gy HDR brachytherapy (n = 46) or 50 Gy wide-field electron radiation (n = 17). The locoregional control rate was 100% in each arm and the 3-year probabilities of cancer-specific and relapse-free survival were 98.1% and 98.4% in the whole-breast radiation group and 100% and 94.4% in the brachytherapy group, respectively. There was no significant difference in outcome or in the incidence of radiation side effects between the 2 treatment arms; however, because of the small number of patients in each arm, it may not be powered to detect a difference. More prospective randomized data will be required to confirm this. Table 3 summarizes HDR and LDR brachytherapy as sole radiation modality after breast-conserving surgery.[65-70,72,73,75]

The current experience using brachytherapy for PBI is promising but still limited. The American Brachytherapy Society published guidelines on the use of brachytherapy for

breast cancer, which emphasized the importance of patient selection, careful treatment planning, and use of DVHs and dose homogeneity index.[76] Nevertheless, brachytherapy has several disadvantages compared with external-beam RT, most importantly its invasiveness. Also, if LDR brachytherapy is delivered, the patient has the additional requirement of an isolation room during treatment delivery. Moreover, long-term cosmetic results are not yet available, and the risk of fibrosis and induration at the implant site remains a concern, especially because it can become quite difficult to routinely examine the treated breast.[65,77,78]

External-Beam Techniques. An external-beam approach is likely to be more acceptable to the patient, to be more widely reproducible, to generate improved dose homogeneity, and to result in better cosmetic results compared with brachytherapy techniques. Additionally, it can be made available at any institution with a linear accelerator facility and spare the health care costs of an extra surgical procedure and several days of hospitalization (in the case of LDR brachytherapy).

The first and only randomized trial of partial-breast external-beam radiation versus whole-breast radiation is the Christie Hospital Breast Conservation trial, a trial of 708 patients that included tumors ≤ 4 cm in size with infiltrating ductal and lobular histologies.[79] After lumpectomy, patients were randomized to undergo RT to the tumor bed only (limited-field [LF] group) or to the whole breast and regional nodes (wide-field [WF] group). No systemic therapy was given in either arm. Results of this trial at 8-year actuarial follow-up (median follow-up, 65 months) suggest that the histologic type of the original breast cancer affected local control. In fact, for infiltrating ductal carcinoma, the actuarial breast recurrence rate was 15% for LF radiation versus 11% for WF radiation, whereas for infiltrating lobular carcinoma, the recurrence rates were 34% for LF radiation and 8% for WF radiation. Moreover, in patients with extensive ductal carcinoma in situ, high recurrence rates of 21% (LF group) and 14% (WF group) were also noted. Lumpectomy with LF radiation was feasible; however, the study identified potential patients at higher risk for local recurrence when treated by PBI.

Formenti et al pilot-tested a phase I feasibility study of hypofractionated conformal external-beam RT to the tumor bed in selected postmenopausal women with T1 breast cancers.[80] The rationale for the study was based on the assumption that a few large fractions can be safely delivered to breast cancers provided that the target volume is sufficiently small and the radiation technique assures maximum sparing of the surrounding normal tissue. Using the radiobiologic linear-quadratic cell survival model with an alpha-beta value for breast carcinoma of 4, a dose of 30 Gy in 5 fractions of 6 Gy per fraction over 10 days was found radiobiologically equivalent to a standard dose of 60 Gy in 30 fractions of 2 Gy. The biologic equivalent dose for late breast tissue complications (including desquamation, fibrosis, erythema, and telangiectasia) was less than or equivalent to that of the standard 60 Gy fractionation. The treatment was found to be feasible in 9 of 10 consecutive patients. At a minimum follow-up of 3 years, there were no recurrences and the patients had "good to excellent" cosmetic results. The technique used was derived from a radiosurgical model of delivering external-beam radiation by multiple noncoplanar fields directed toward the tumor bed while sparing as much of the normal tissue as possible.[81] Immobilization of the patient in prone position on a dedicated breast board allowed the breast tissue to freely fall through an opening in the board and reduced to a minimum the motion of the target caused by breathing.

Based on the initial pilot study, a phase I/II study funded by a grant from the Department of Defense (DAMD 17-01-1-0345) is currently ongoing. Currently, 47 of 99 planned patients have been accrued to the study, which consists of a regimen of hypofractionated PBI, 30 Gy in 5 fractions over 10 days.[82] The volume of breast tissue irradiated is the surgical cavity, which is defined at planning computed tomography as the area of postoperative architectural distortion, in conjunction with information derived from mammographic and pathologic findings (Figure 2B). Forty-six of the 47 patients completed treatment with only mild acute toxicity (grade I/II skin toxicity). One patient refused further treatment after 2 fractions with no acute toxicities, but discontinued for personal reasons. At a median follow-up of 17 months (range, 1-39 months), no local recurrences have occurred as of yet. Whereas, in the initial report, 1 of 10 patients could not be treated via the original fractionated radiosurgery-like technique because of the proximity of the lesion to the chest wall. In the next series of 47 patients, the predominant treatment technique was a pair of parallel-opposed mini-tangents.

Baglan et al also piloted a phase I/II study of accelerated PBI in 9 patients.[83] Their technique and dose fractionation differed from that used by Formenti et al in that they treated patients in supine position using an active breathing control method to account for breast movement related to respiratory excursion. Additionally, the model of dose fractionation appeared to be extrapolated from the brachytherapy dose fractionation schedules of 34 Gy in 10 fractions b.i.d. over 5 days in 5 patients, followed by 38.5 Gy in 10 b.i.d. fractions over 5 days in the remaining 4 patients. The technique appeared to be feasible and well tolerated.

Finally, intraoperative RT using a linear accelerator electron beam has been investigated by the European Institute of Oncology at the University of Milan, Italy, which uses a linear accelerator with a robotic arm in an operating room, which delivers electron beams of varying energies: 3, 5, 7, and 9 MeV. The radiation beam is collimated using a Perspex tube.[84] A pilot phase I trial tested different single radiation doses from 10 to 21 Gy after initial quadrantectomy with 1-2 cm clear margins and initial results estimated that a single 21-Gy fraction is radiobiologically equivalent to 60 Gy in 30 fractions in terms of tumor control. However, the initial results of 101 patients were reported with a short median follow-up of 8 months (range, 1-17 months) and concern remains about the effect of such a large single dose on long-term complications, including fibrosis, telangiectasia, and fat necrosis. Advantages of the technique are the even dose distribution achieved by electron-beam RT compared with brachytherapy and the rapidity and potential cost effectiveness of a single treatment.

Research on Genetic Determinants of Long-Term Toxicity

One of the concerns of using larger doses per fraction for breast RT is the potential adverse effects on cosmesis caused by RT-induced fibrosis and skin telangiectasia.[46,48] Current-

ly, no established markers are available for integration to routine practice to predict which group of patients will develop long-term complications. However, in the future, the recognition of genetic predispositions to these complications will enable the exclusion of high-risk carriers from the trials of accelerated/hypofractionated radiation. In other words, similar to the impact of pharmacogenomics in medical oncology, the field of radiation genomics is also rapidly emerging, permitting identification of individuals with genetic predisposition to inferior repair of the damage caused by ionizing radiation. For instance, relevant genetic polymorphisms have started to emerge, including transforming growth factor (TGF)–β1 single-nucleotide polymorphism[85] and mutations of the ataxia telangiectasia mutated (ATM) gene,[86] which have been associated with individuals who were found to have moderate to severe long-term RT-induced complications.

Quarmby et al investigated whether TGF-β1 single-nucleotide polymorphisms were associated with the susceptibility of patients with breast cancer to severe radiation-induced normal tissue damage.[85] They performed polymerase chain reaction–restriction fragment length polymorphism assays for TGF-β1 gene polymorphisms on DNA obtained from 103 patients with breast cancer who received RT. The G-800A, C-509T, T+869C, and G+915C polymorphic sites were examined, and genotype and allele frequencies of 2 subgroups of patients were calculated and compared. The investigators found that the less-prevalent –509T and +869C alleles were significantly associated with a subgroup of patients who developed severe radiation-induced normal tissue fibrosis (n = 15) compared with those who did not (n = 88; odds ratio = 3.4 and $P = 0.0036$; odds ratio = 2.37 and $P = 0.035$, respectively). Furthermore, patients with the –509TT or +869CC genotypes were 7-15 times more likely to develop severe fibrosis. These findings imply a role for the –509T and +869C alleles in the biologic mechanisms underlying susceptibility to radiation-induced fibrosis.

Ianuzzi et al showed a significant correlation between ATM gene status and the development of grade 3/4 subcutaneous late effects in breast cancer by using denaturing high-performance liquid chromatography, a powerful technique in detecting missense mutations and small deletions and insertions.[86] All 3 patients who manifested grade 3/4 subcutaneous late sequelae possessed 2 ATM genes, whereas only 3 of the 43 patients (7%) who did not develop this form of severe toxicity harbored an ATM gene ($P = 0.001$). In contrast, none of the 3 ATM gene carriers who had a single mutation developed a severe subcutaneous reaction.

The future may hold even greater capacity to tailor RT dose–volume fractionation schemes. If fibrosis-associated polymorphic sites in other genes could be identified, it may be possible to detect fibrosis-prone individuals with greater certainty before RT.

Conclusion

Most novel approaches to postoperative RT as part of BCT have included accelerated breast irradiation (ABI). Accelerated breast irradiation to the whole breast or partial breast remains a research approach, as level 1 evidence is currently unavailable to prove its equivalence to standard postoperative RT. Many unresolved issues remain, including optimal patient selection, optimal determination of treatment volume, the ideal dose-fractionation schedule, and total dose. One of the limitations of the external-beam techniques, especially when IMRT is used, is that the integral dose to the remaining breast tissue is higher with increasing number of fields. In addition, for women undergoing partial-breast RT, practically no information exists regarding potential salvage of recurrences after ABI. Finally, the best sequencing pattern with chemotherapy and the ability to perform salvage therapy after ABI also need to be established. However, because of its potential high impact on the care of most patients with breast cancer, ABI should be a research priority in this disease.

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NYU prone PBI training course

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Tamara Duckworth

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Silvio Remon
John Belanich and Tillie Russo

(original work was supported by DOD IDEA GRANT DAMD17-01-1-0345)

NYU 00-23: prone accelerated breast irradiation (PABI)

Protocol for simulation, planning and treatment

IDEA GRANT DAMD17-01-1-0345

Table 1. Study schema for Stage I breast cancer postmenopausal, nonpalpable tumors, after segmental mastectomy

	Informed consent	Blood collection for TGF-β
	CT planning in prone position, determination of tumor bed and ipsilateral breast tissue	
Days 1–10	Conformal tumor bed radiotherapy 6 Gy × 5 fractions in 2 wk Days 1, 3, 5, 8, 10 (total dose, 30 Gy)	
Day 10	Last day of treatment	Blood collection for TGF-β

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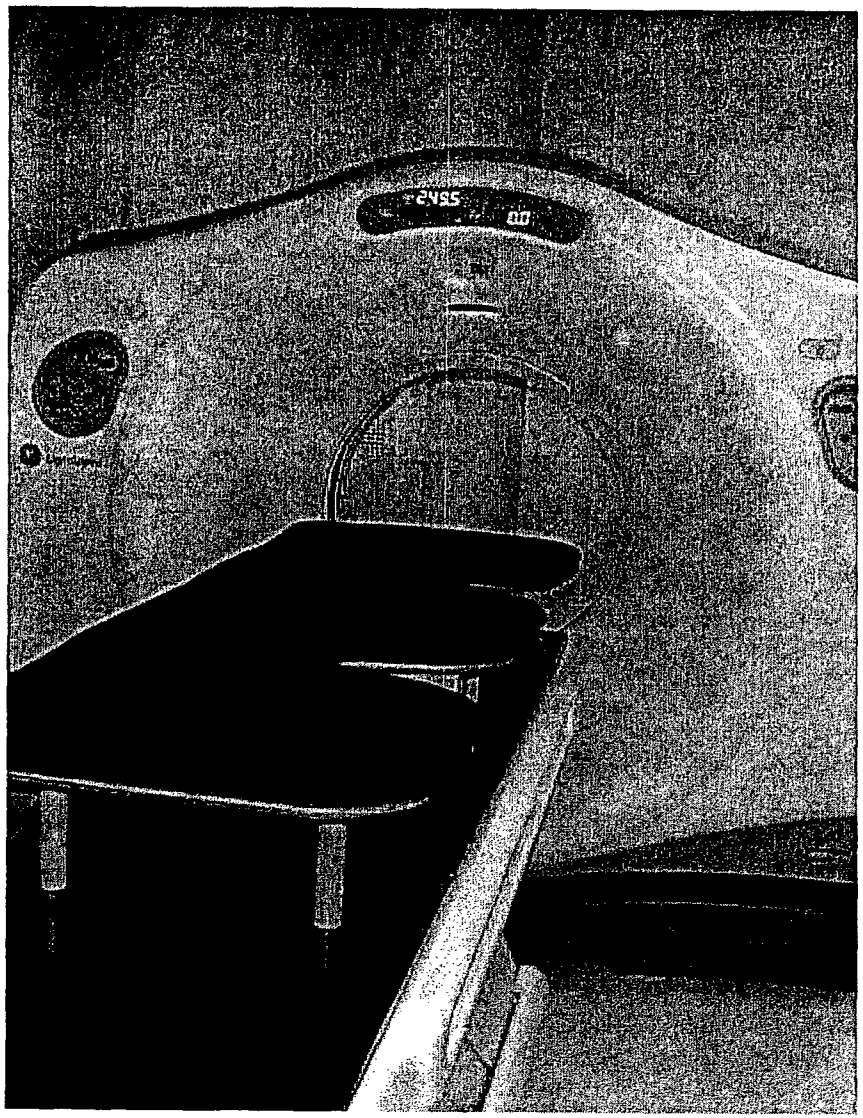
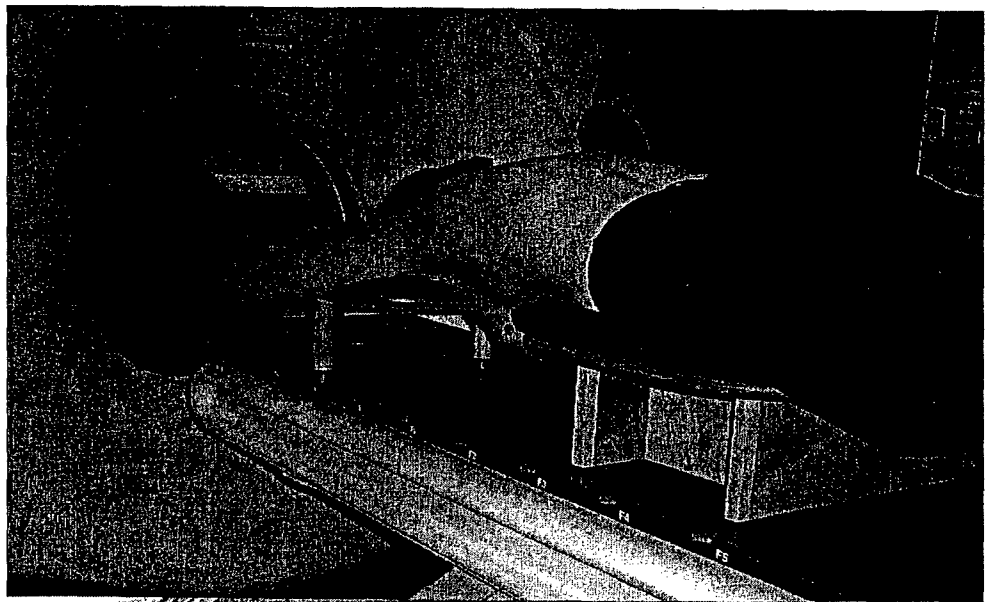
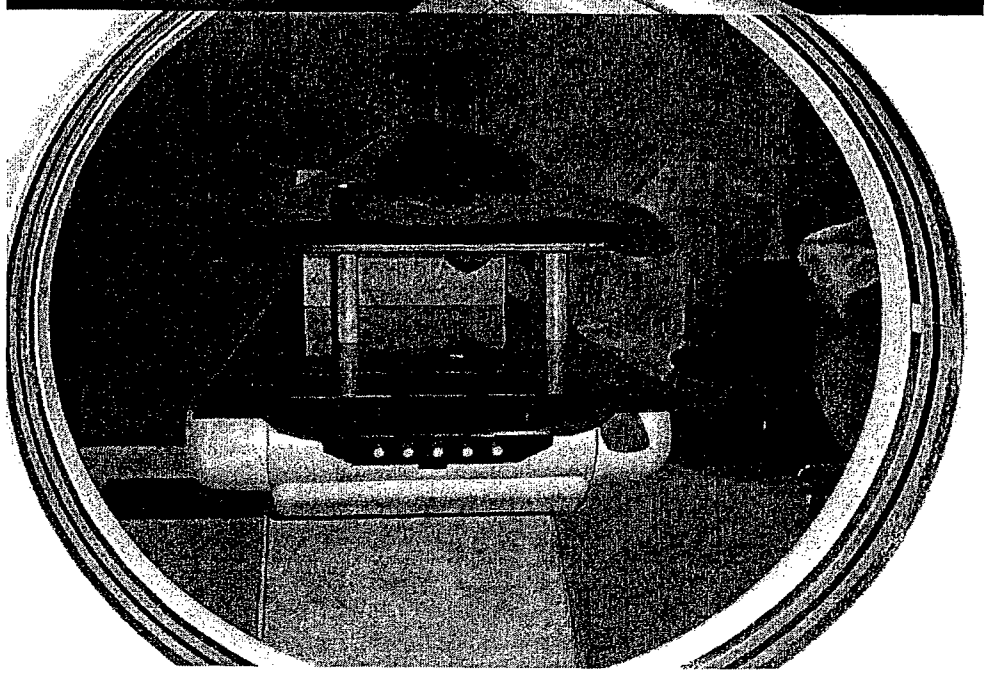
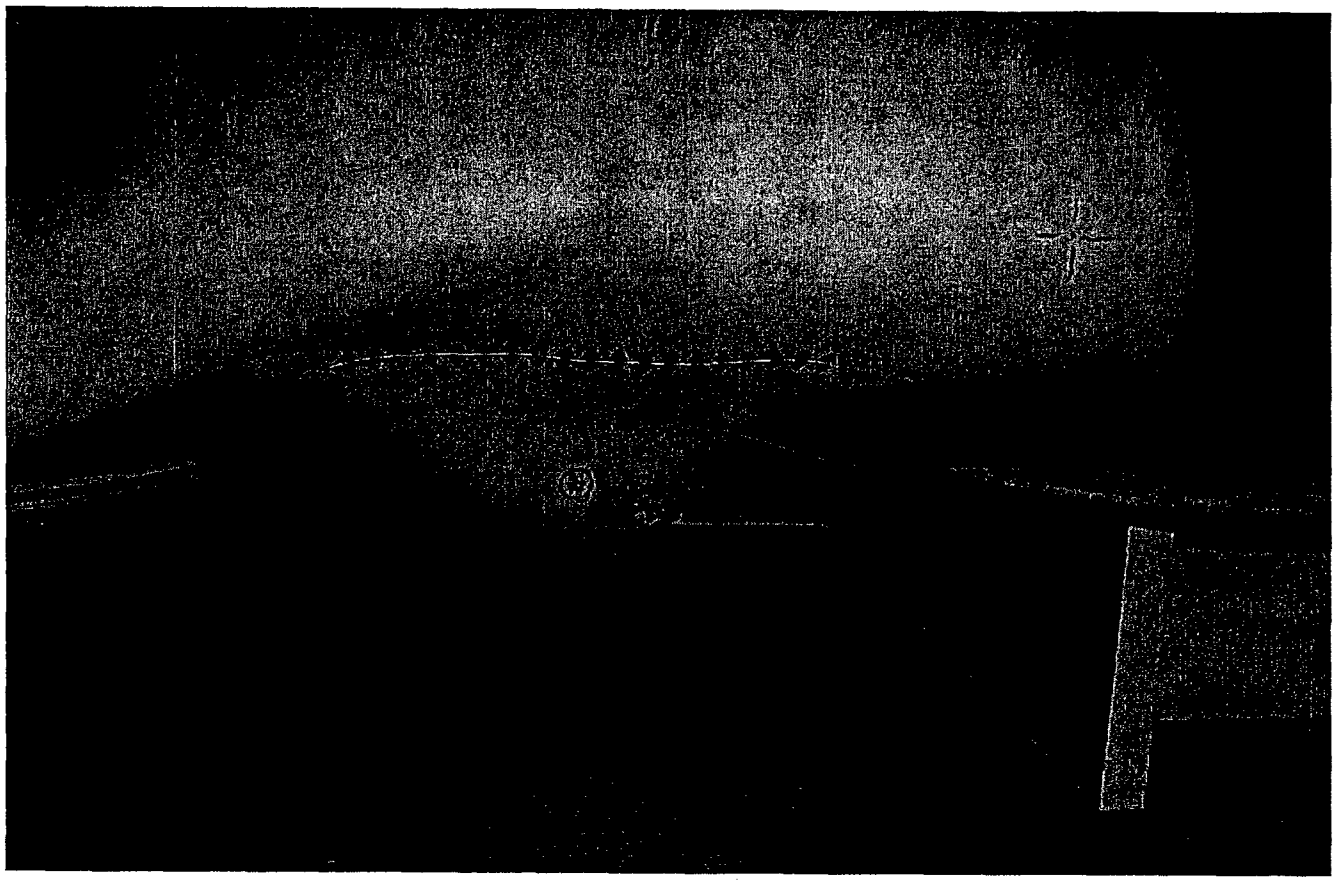
Prone Breast CT







Prone set-up



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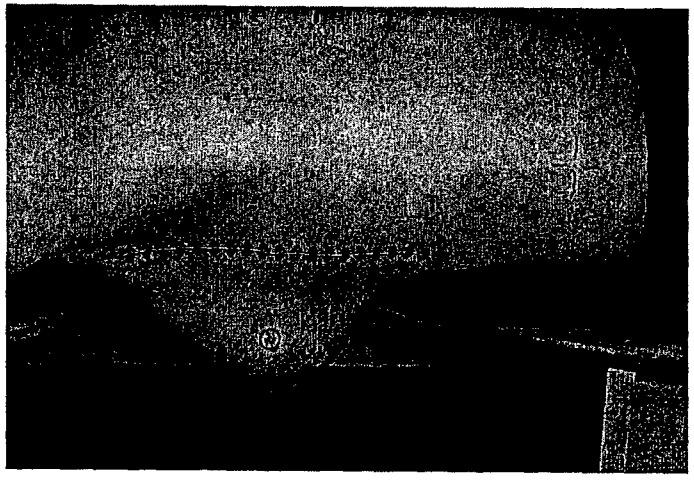
Prone set-up protocol

1. Patient set up supine for placement of marks to define breast tissue as per conventional breast tangents.

2. Patient with marks is positioned prone on a dedicated table

3. Laser marks are recorded at the waist level (leveling marks)

4. Triangulation marks on back torso, axillary line and breast tissue are placed with the help of lasers, to identify a plane orthogonal to the table that also crosses the tumor cavity



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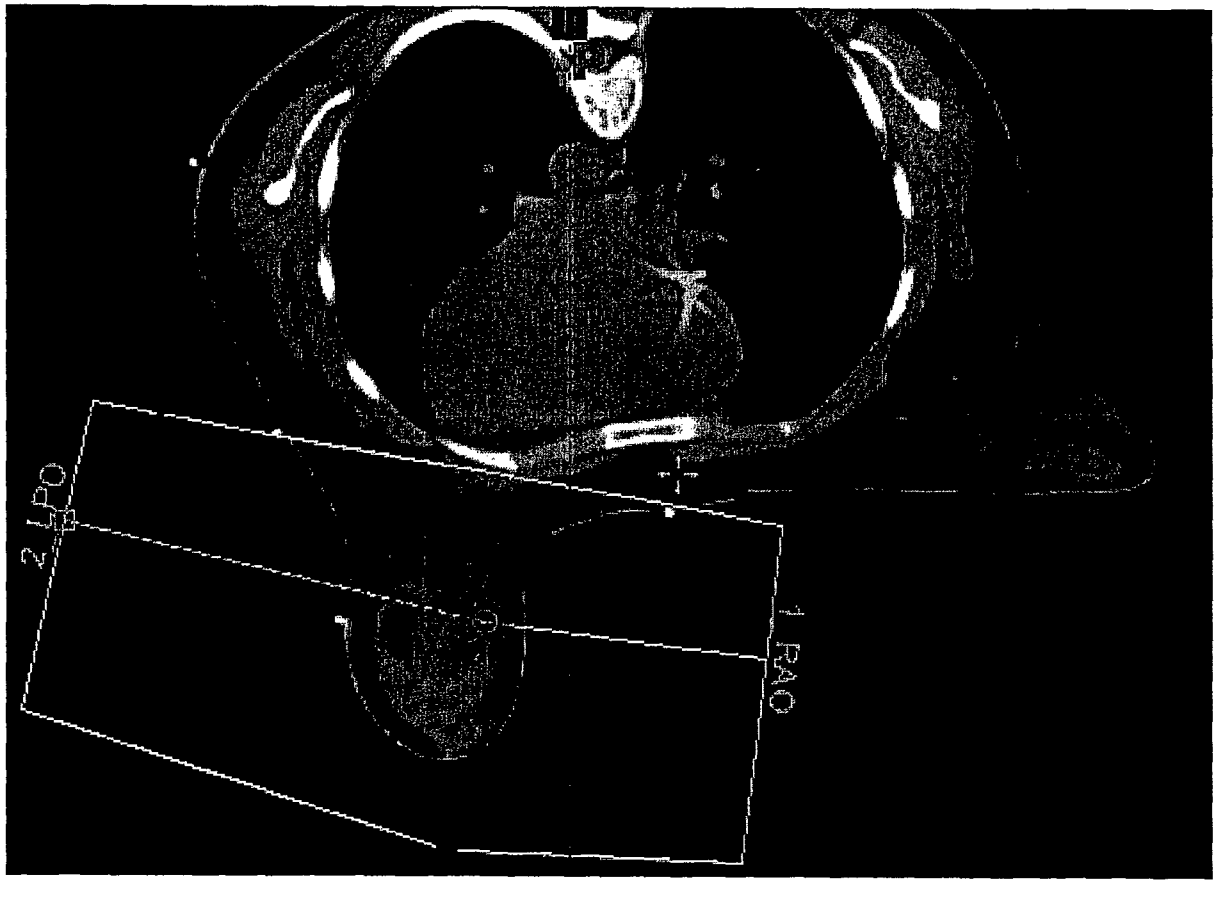
Plane identification for triangulation



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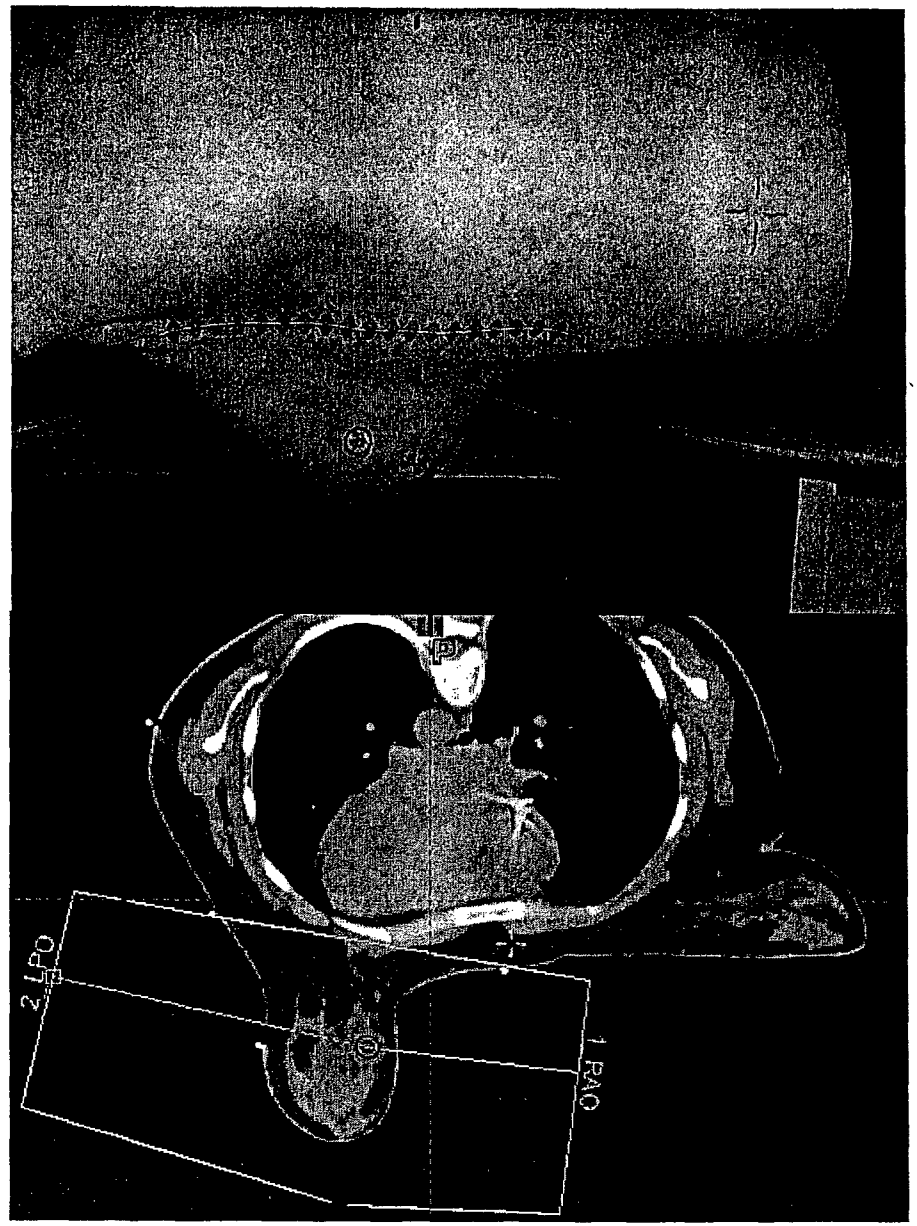
Prone set-up protocol

5. Non contrast CT images are acquired at 3.75 mm thick intervals from the mandible to below the diaphragm using a GE light speed helical CT scanner

6. During CT simulation the plane of reference is verified by visualizing the four "bee bees" in the same CT cut
   Four tattoos permanent dots are then placed.

7. CT images are transferred to a Varian Eclipse treatment planning system.



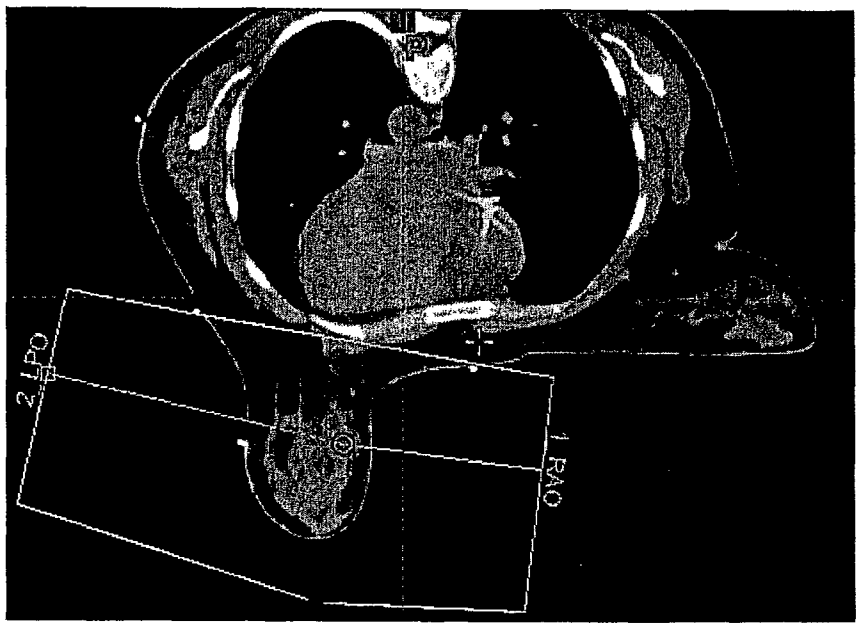
Prone set-up protocol

8. Radiation oncologist outlines contours to define relevant volumes:

    1. Ipsilateral breast tissue (IBV)
    2. Tumor cavity (CTV)
    3. Heart
    4. Lung
    5. (axillary nodes)

9. PTV is defined as the CTV +1.5-2 cm margins.

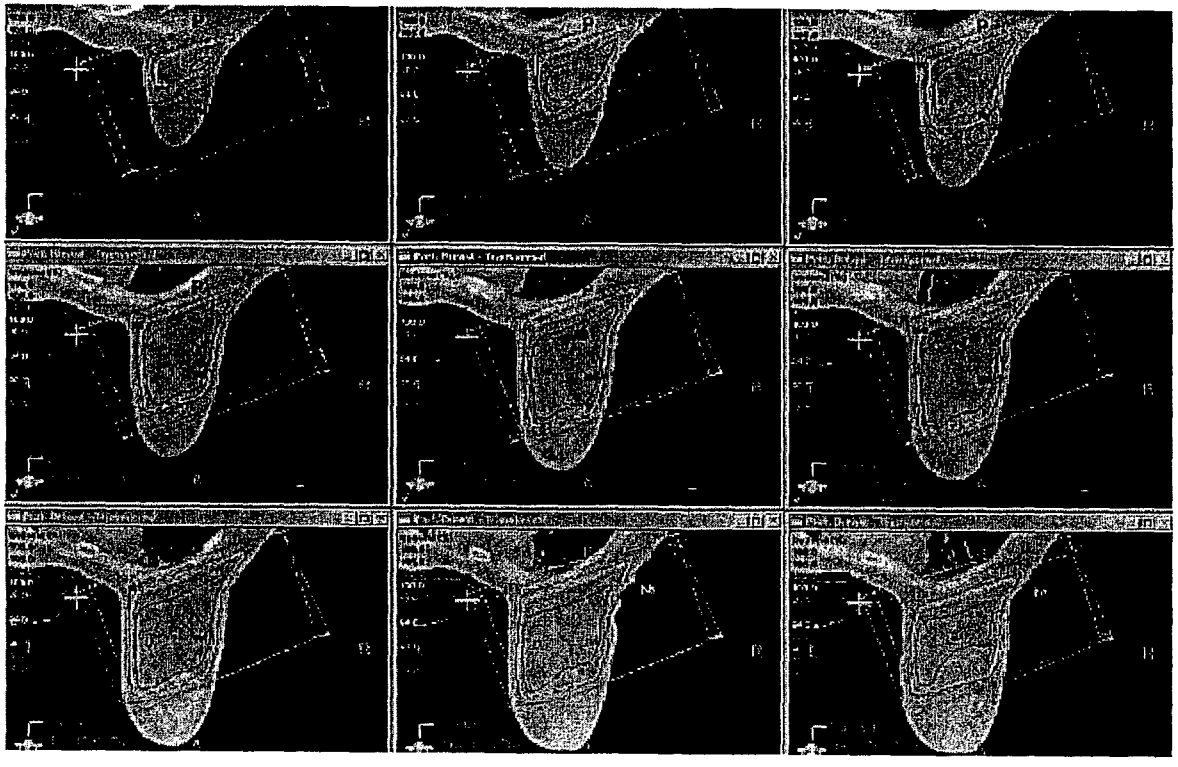
    After uniform expansion the PTV is limited anteriorly by the skin and posteriorly by the chest wall. An additional 7 mm margin is added to the PTV to account for beam penumbra for a **total margin of 2.2-2.7 cm.**



Prone set-up protocol

10. After Placing the isocenter
    4-7 cm from midline on an axis that passes through the center of the PTV, the physicist selects an optimal field arrangement to deliver the prescribed dose.
    Fields are designed to miss contralateral breast, heart and lung completely.

11. The dose is normalized at the isocenter by choosing an isodose surface that encompasses the PTV, typically 95%.
    Dose inhomogeneity is kept <110%.



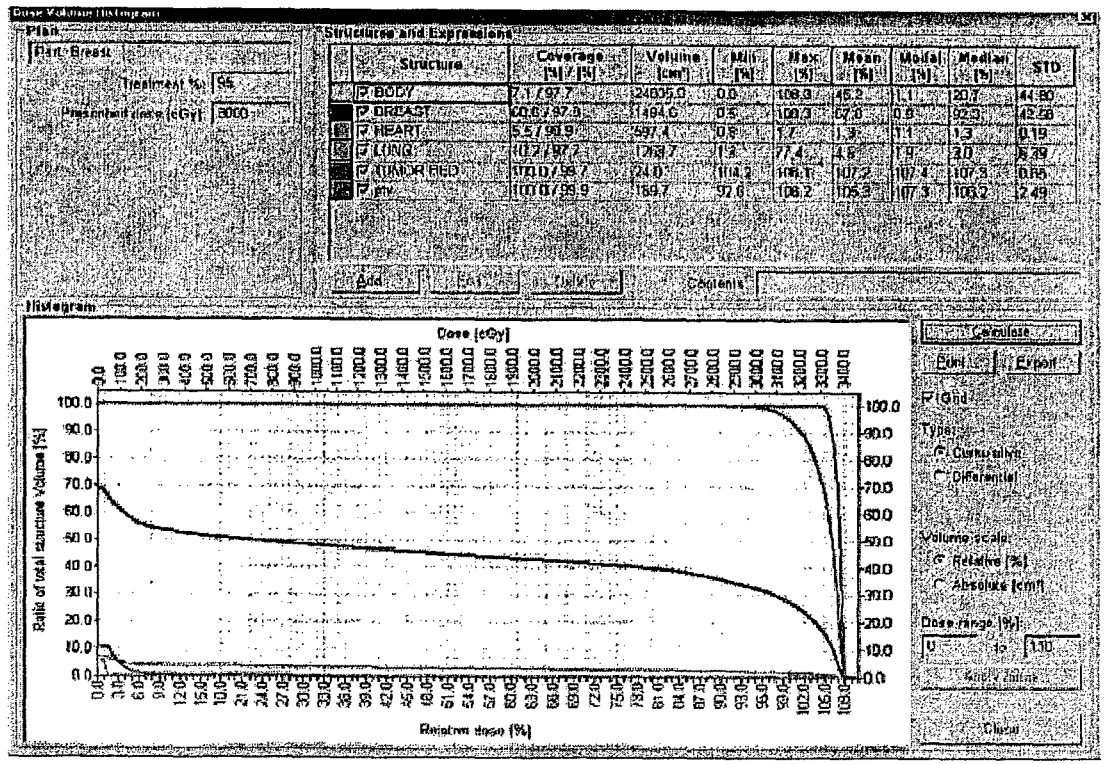
Prone set-up protocol

Tissue dose guidelines are:

1. 50% of the IBV to receive <50% of dose
2. < 10% of heart and lung volume to receive any significant dose

13. DVH are obtained for:
    1. Ipsilateral breast tissue (IBV)
    2. Tumor cavity (CTV)
    3. PTV
    4. Heart
    5. Lung

14. Portal imaging is done for each treatment.



NYU 00-23: prone accelerated breast irradiation (PABI)

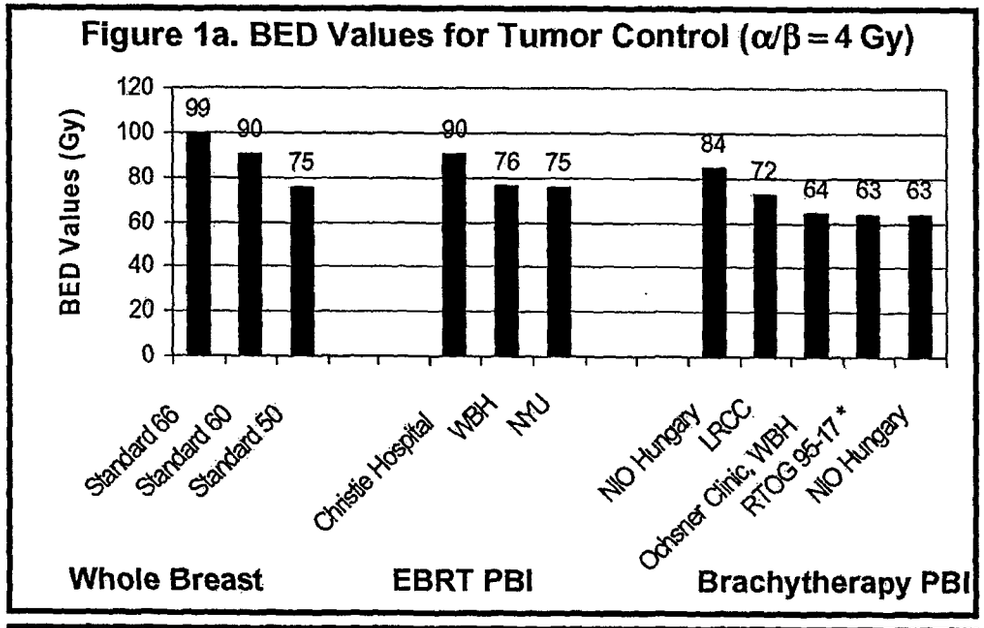
Rationale for dose/fractionation

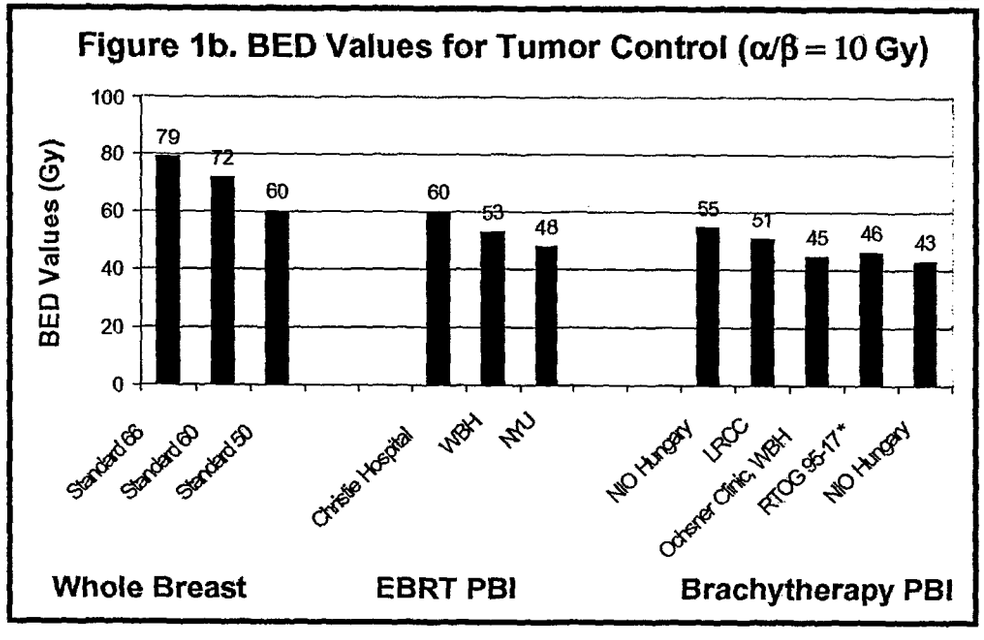
Biologically Effective Doses (BED)

	α/β (Gy)	BED Standard 60 Gy/30 fx	BED Standard 50 Gy/25 fx	BED Hypofractionated 6 Gy/5 fx
Erythema	8	75 Gy_8	63 Gy_8	53 Gy_8
Desquamation	11	71Gy_{11}	59 Gy_{11}	46 Gy_{11}
Telangiectasia	4	90 Gy_4	75 Gy_4	75 Gy_4
Fibrosis	2	120 Gy_2	100 Gy_2	120 Gy_2
Tumor	4	90 Gy_4	75 Gy_4	75 Gy_4
Tumor*	4	86 Gy_4	72 Gy_4	75 Gy

*Taking into account cell proliferation during the course of treatment

Int J Radiat Oncol Biol Phys. 2004 Oct 1;60(2):493-504





What is the optimal dose/fractionation ?

Int J Radiat Oncol Biol Phys. 2004
Oct 1;60(5):1393-1404

Int J Radiat Oncol Biol Phys. 2005
Jul 1;62(3):943-944

EORTC trial 22881 update

"On the relative hazard scale, there is no evidence that the effect of the boost treatment on local control depends on age (P=0.871)"

Antonini et al. Proceedings ESTRO 23, Amsterdam 2004, abstract # 281, S126

NYU 03-30: Prone accelerated intensity modulated whole breast radiotherapy (P-AIMRT)

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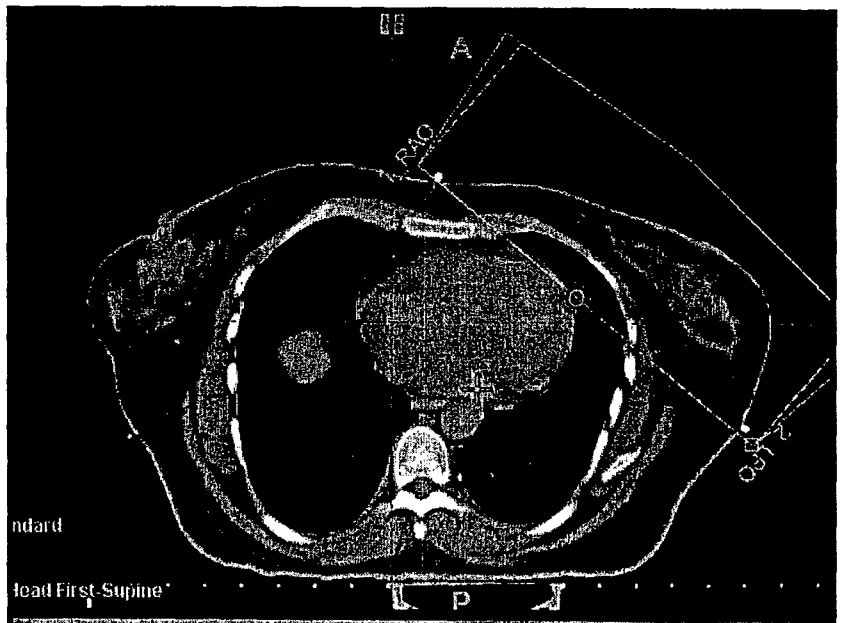

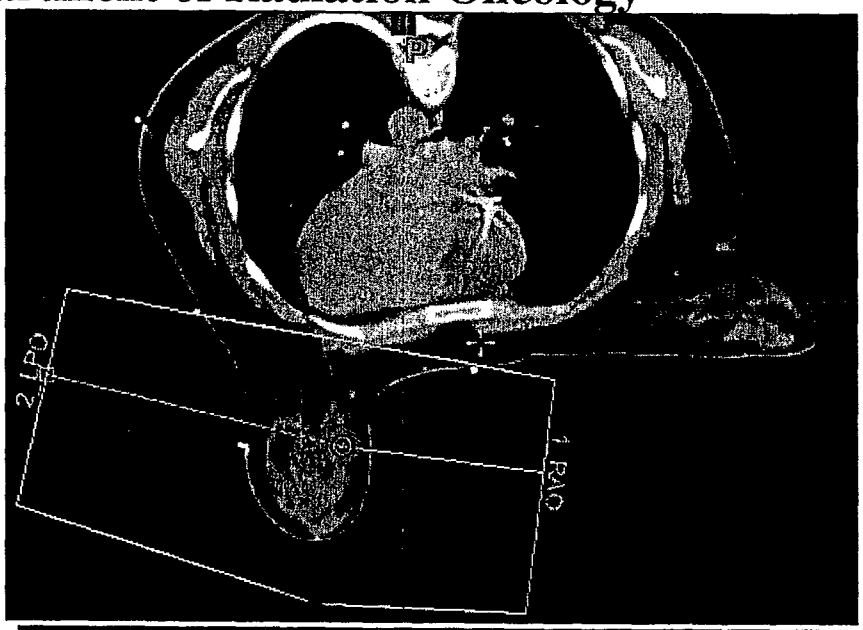

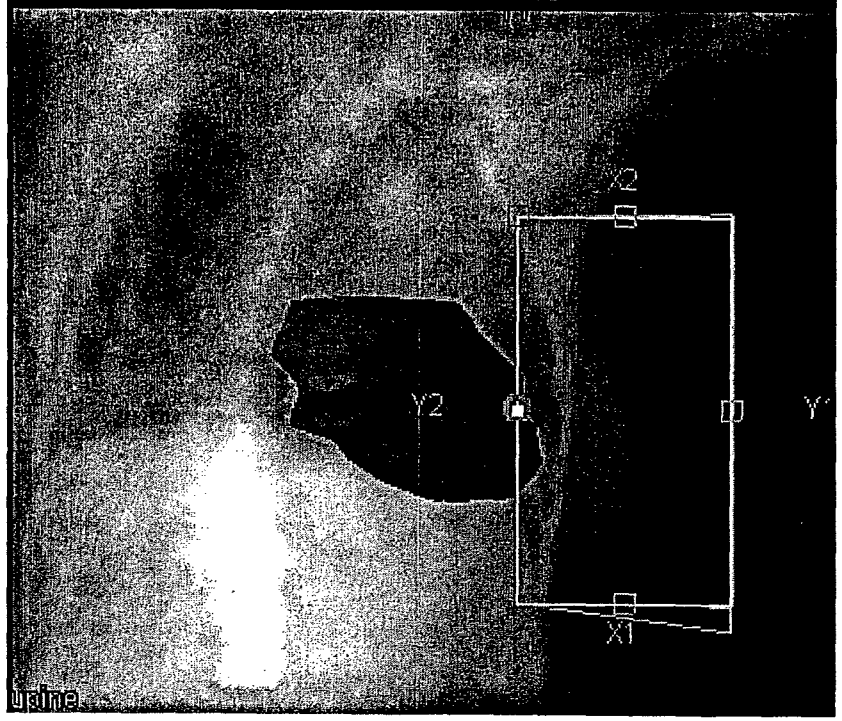

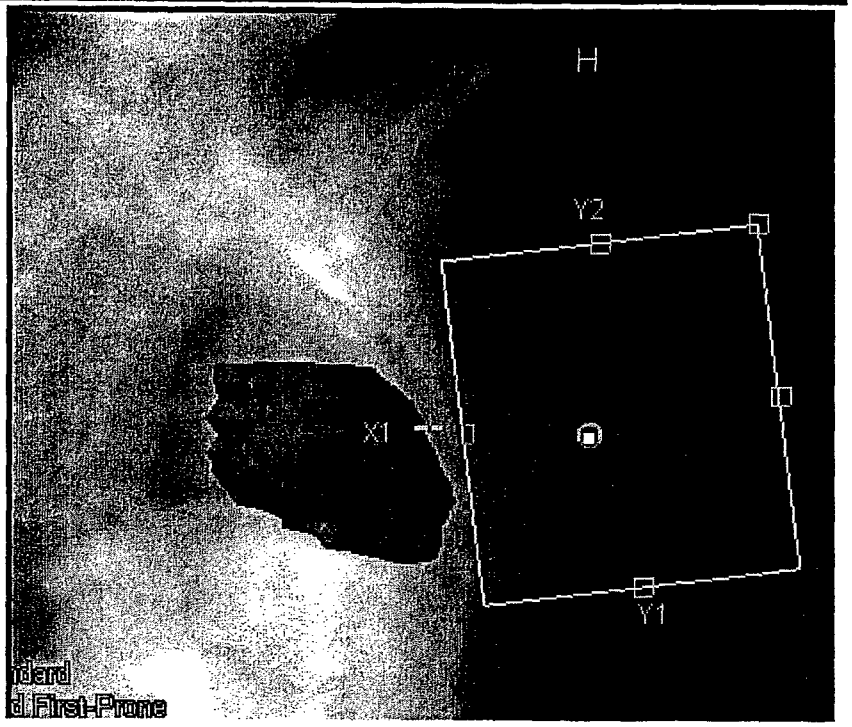

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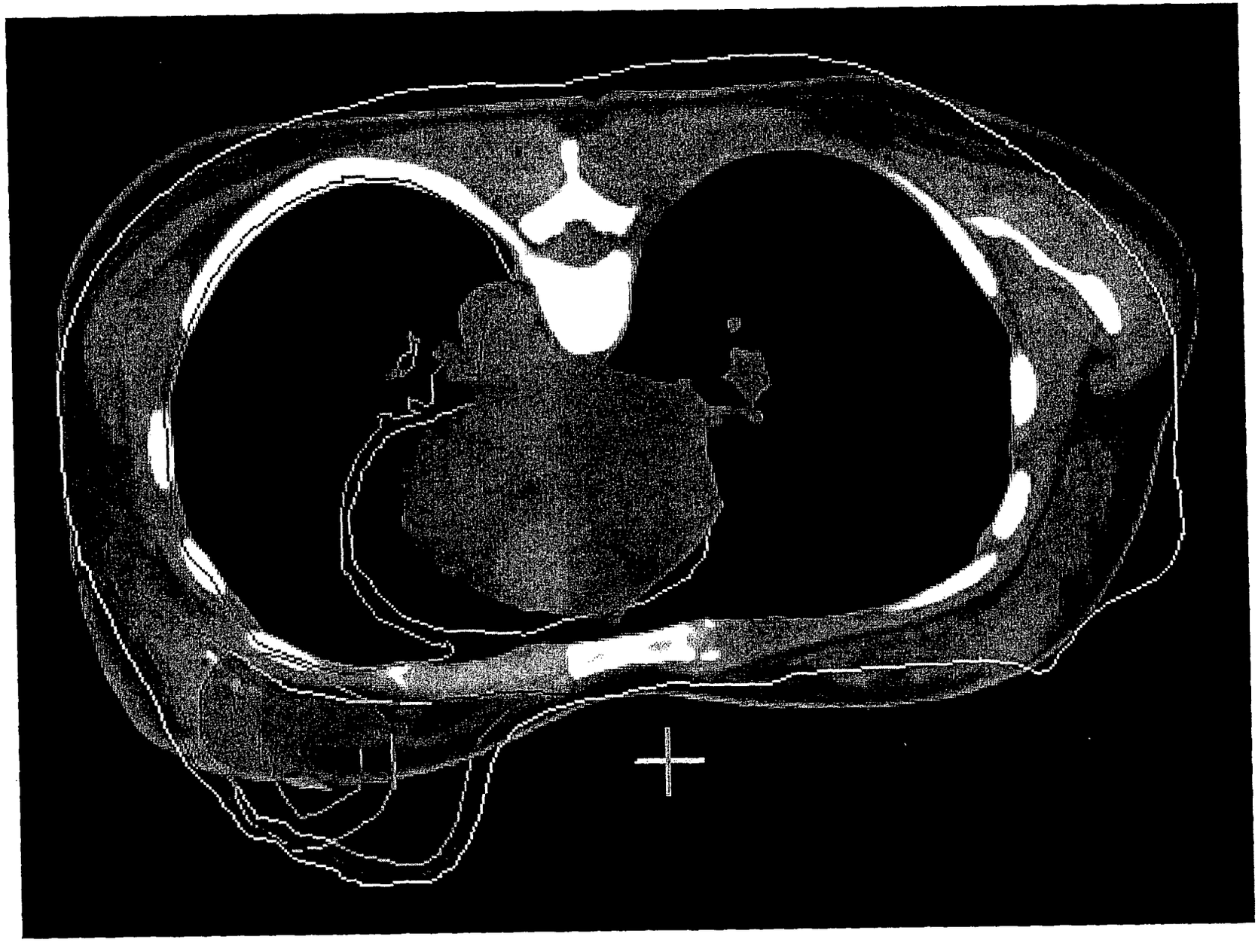
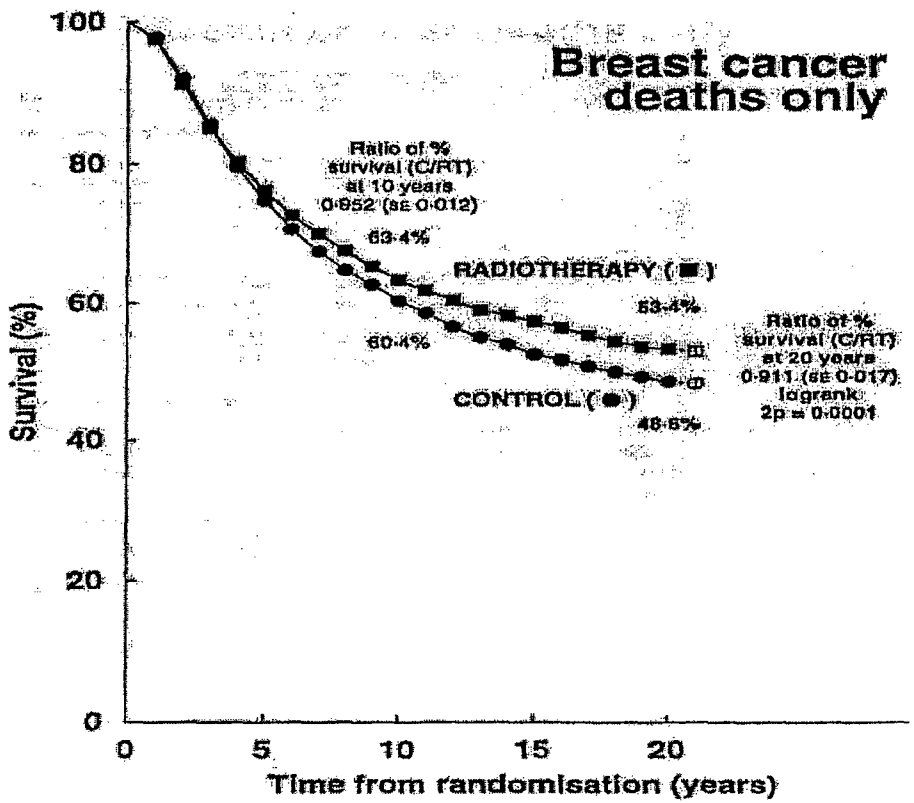
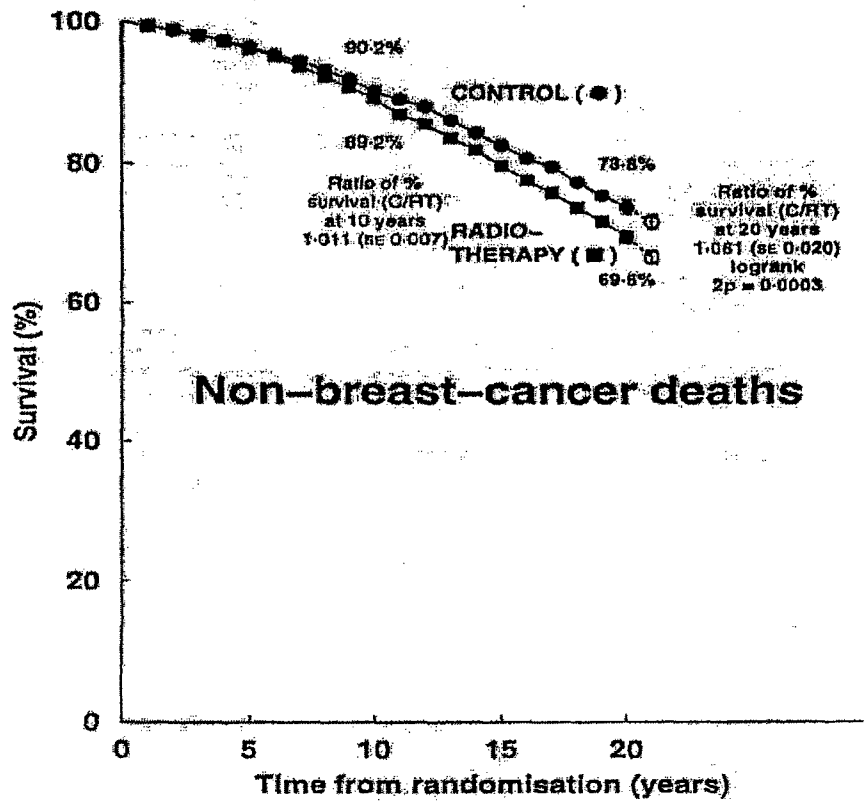


Meta-analisis of 20,000 breast cancer patients in 40 randomized trials, 20 y follow up





↑ RT related vascular mortality: RR 1.3 p = 0.0007

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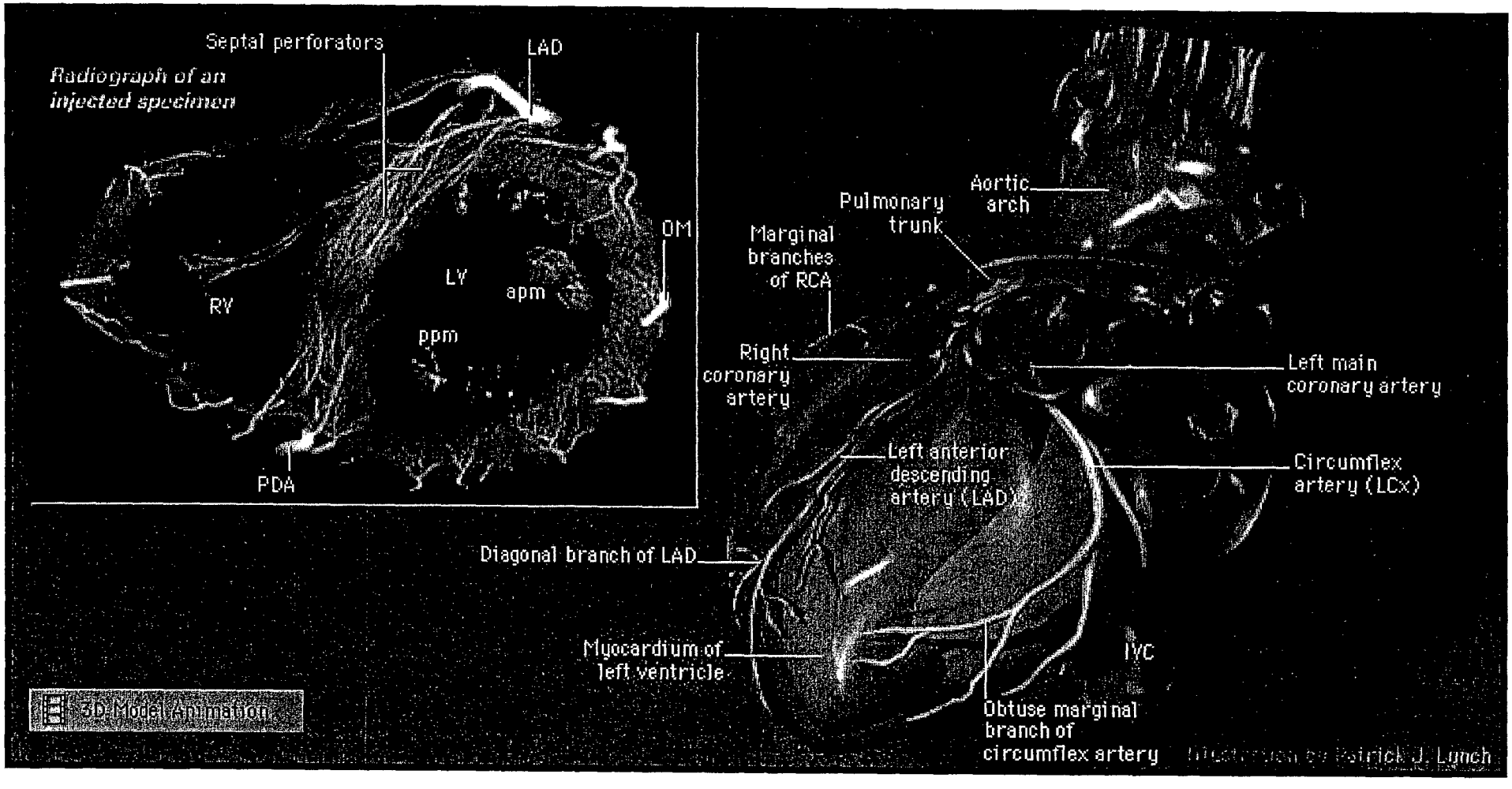
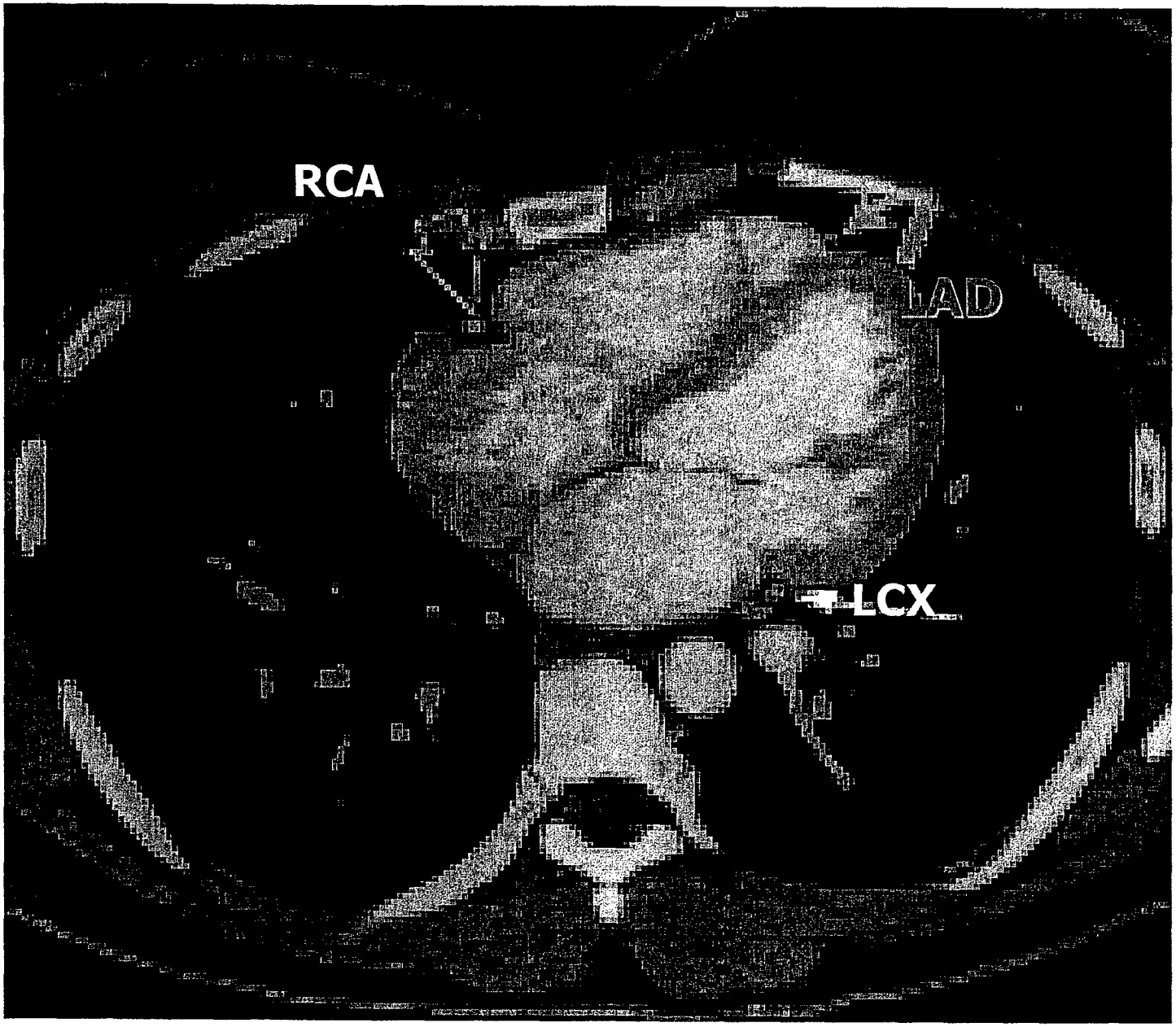
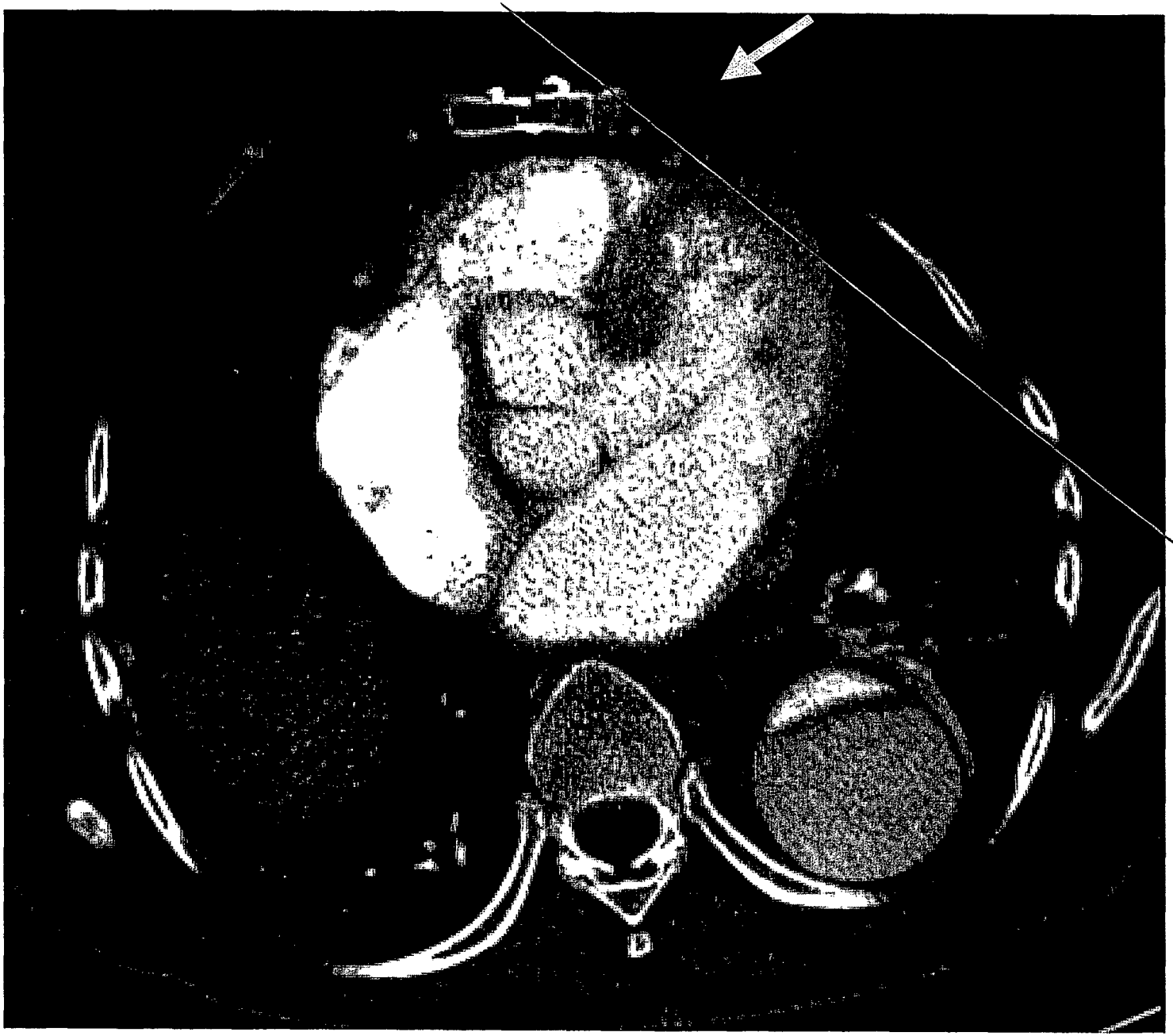
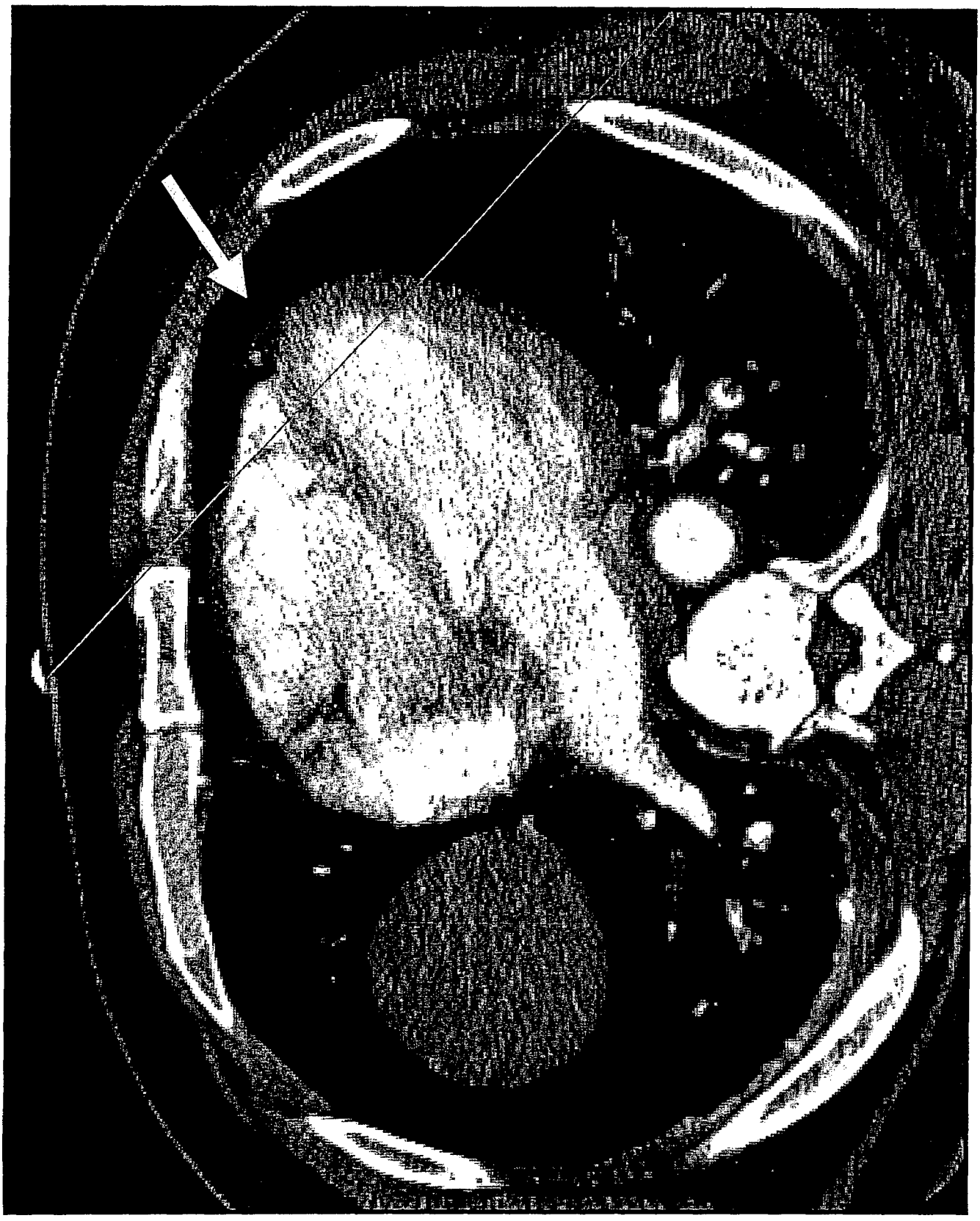



RCA
LAD
LCX





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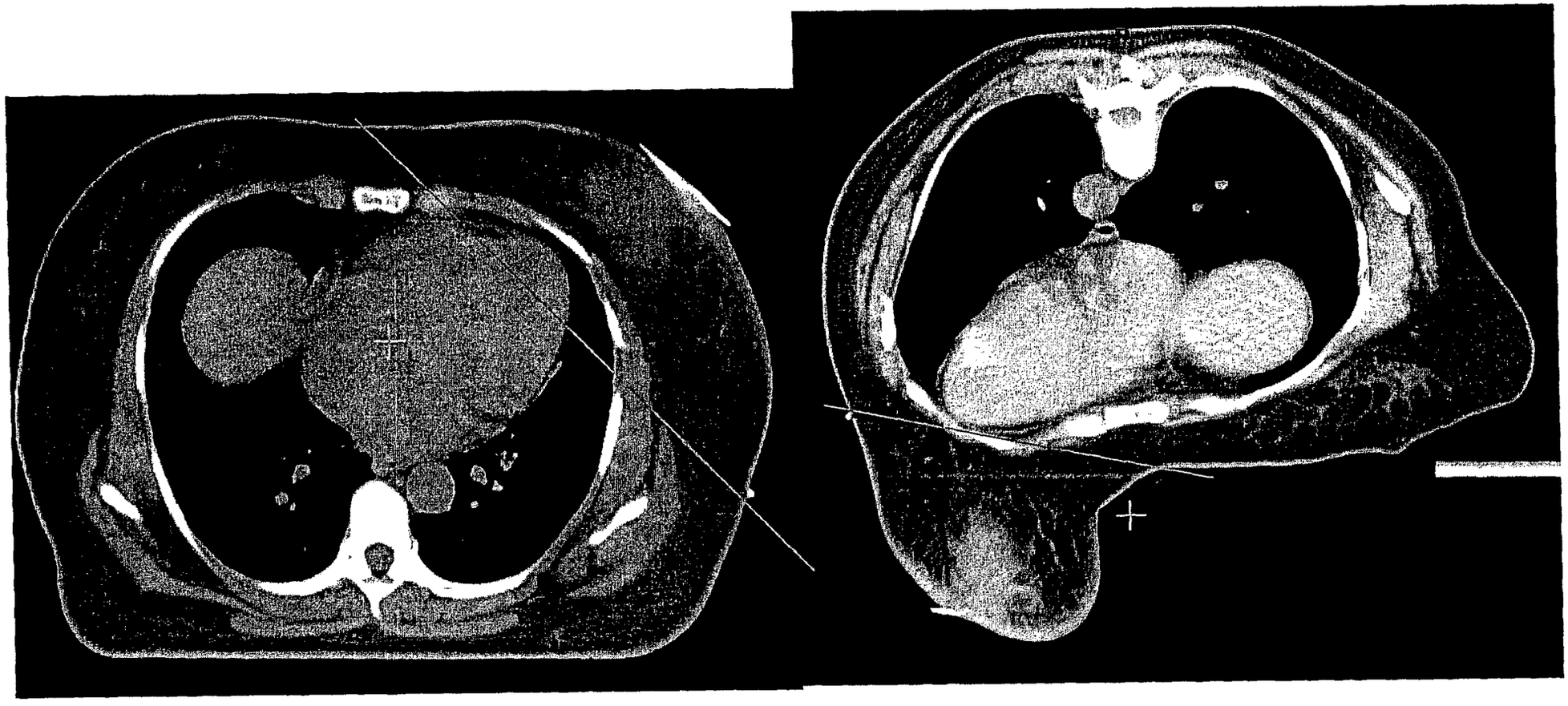
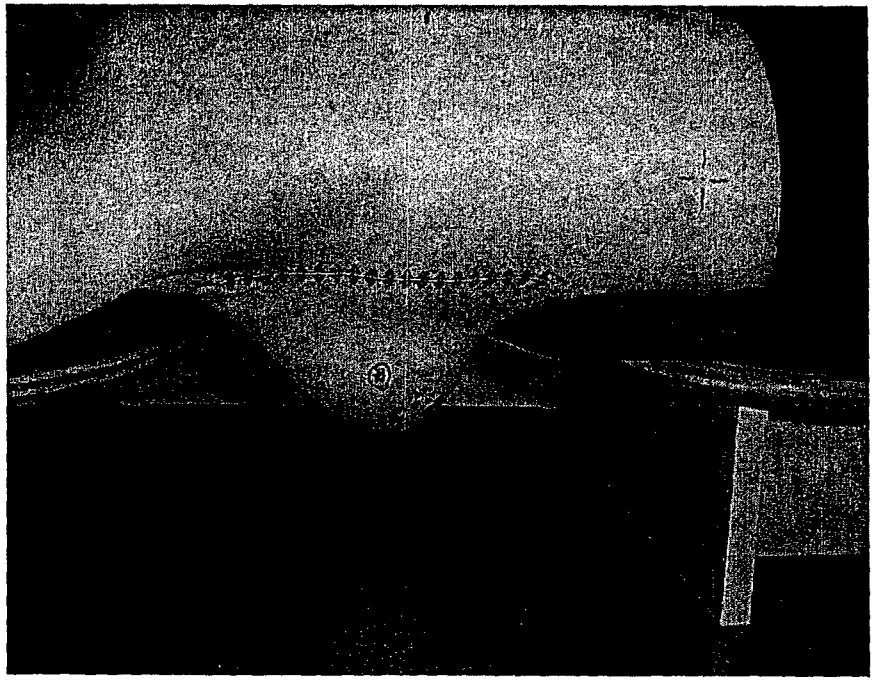
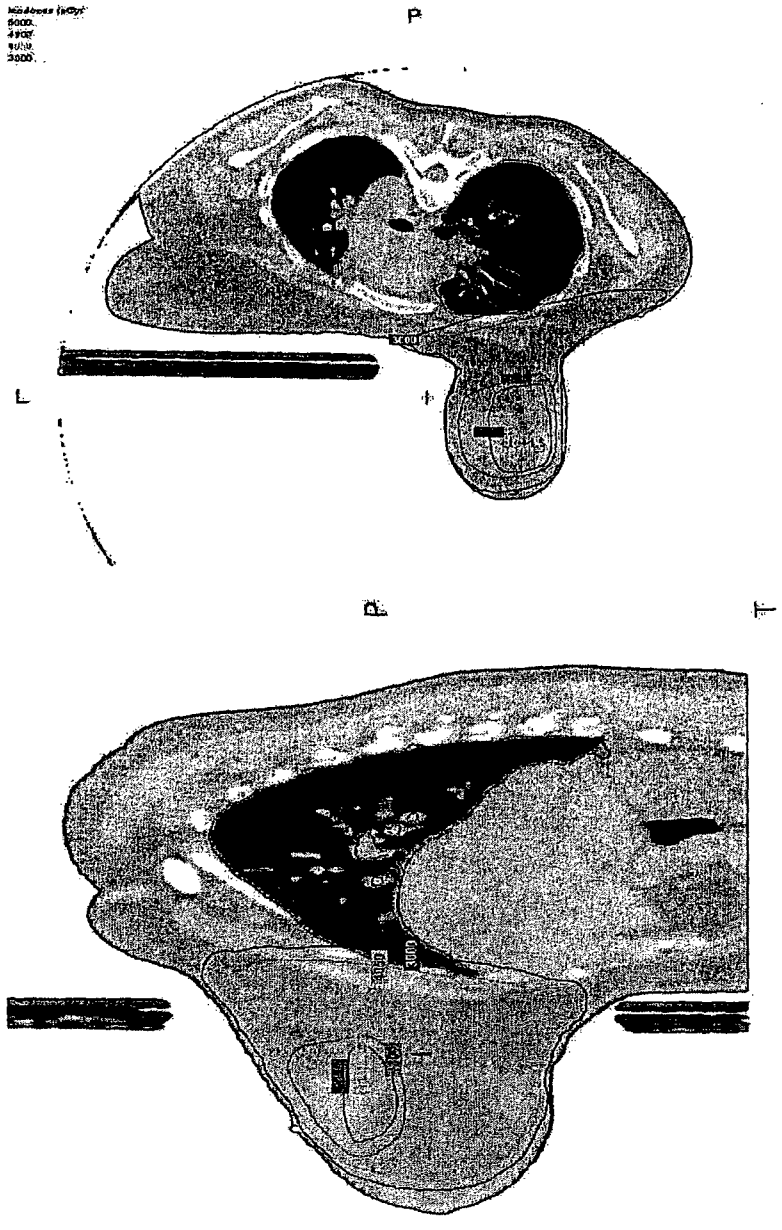


NYU 03-01

Phase I-II Accelerated IMRT trial

2.7 Gy X 15 to the entire breast with a .5 Gy concomitant boost to tumor bed (2.7 +.5 Gy = 3.2 Gy)





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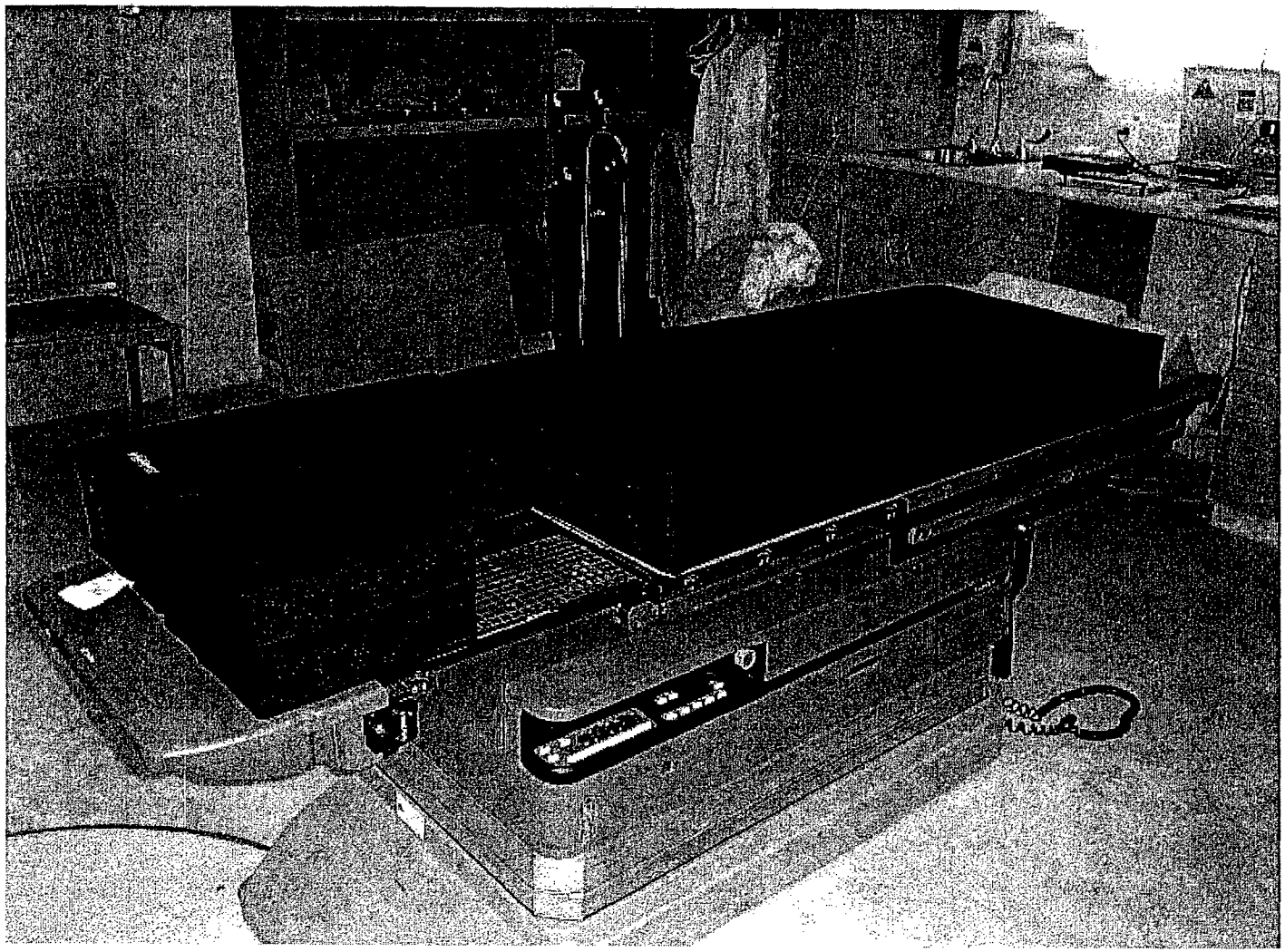

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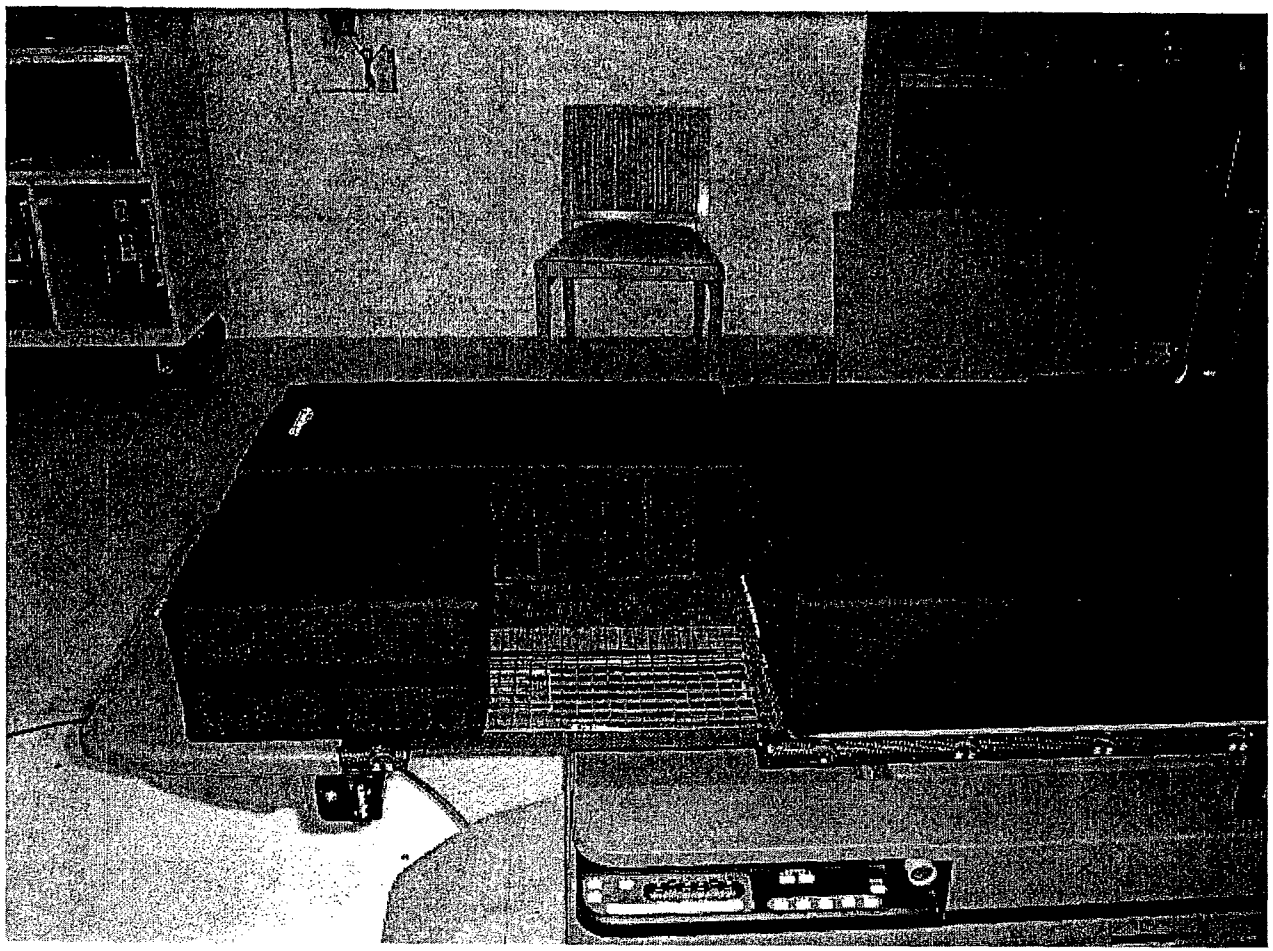

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